IX. EVIDENCE APPENDIX

Attached hereto are the following Exhibits:

A. Taylor *et al.*, United States Patent No. 6,083,257

B. Ecer *et al.*, United States Patent No. 4,486,247

C. Narayanan *et al.*, United States Patent No. 5,336,518

D. Final Office Action of 04 April 2011

E. Non-Final Office Action of 31 August 2010

F. Final Office Action of 24 December 2009

G. Kraus *et al.*, United States Patent No. 6,712,816

H. Non-Final Office Action of 23 June 2009

I. Final Office Action of 16 December 2008

J. Response of 23 October 2009 to the June 2009 Non-Final Office Action

K. Declaration of Dr. Pamela Kramer-Brown under 37 C.F.R. § 132

EVIDENCE APPENDIX

EXHIBIT A

US006083257A

United States Patent [19]

Taylor et al.

[11] Patent Number: 6,083,257

[45] Date of Patent: Jul. 4, 2000

[54] **BRAIDED STENT**

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[73] Assignee: **Biocompatibles Limited**, Surrey, United Kingdom

[21] Appl. No.: **09/011,523**

[22] PCT Filed: **Nov. 1, 1996**

[86] PCT No.: **PCT/GB96/02689**

§ 371 Date: **Apr. 28, 1998**

§ 102(e) Date: **Apr. 28, 1998**

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PCT Pub. Date: **May 9, 1997**

[30] **Foreign Application Priority Data**

Nov. 1, 1995 [GB] United Kingdom 9522332

[51] **Int. Cl.**[7] **A61F 2/06**

[52] **U.S. Cl.** **623/1**; 623/12

[58] **Field of Search** 623/1, 12

[56] **References Cited**

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[57] **ABSTRACT**

A braided stent **(1)** for transluminal implantation in body lumens is self-expanding and has a radial expanded configuration in which the angle α between filaments is acute. Some or all of filaments **(6,7)** are welded together in pairs at each end **(4,5)** of the stent to provide beads **(8)**, thereby strengthening the stent and assisting its deployment from a delivery device. The stent is preferably completely coated using a biocompatible polymeric coating, said polymer preferably having pendant phosphoryl choline groups. A method of making the stent by braiding and welding is described as well as a delivery device for deploying the device.

19 Claims, 4 Drawing Sheets

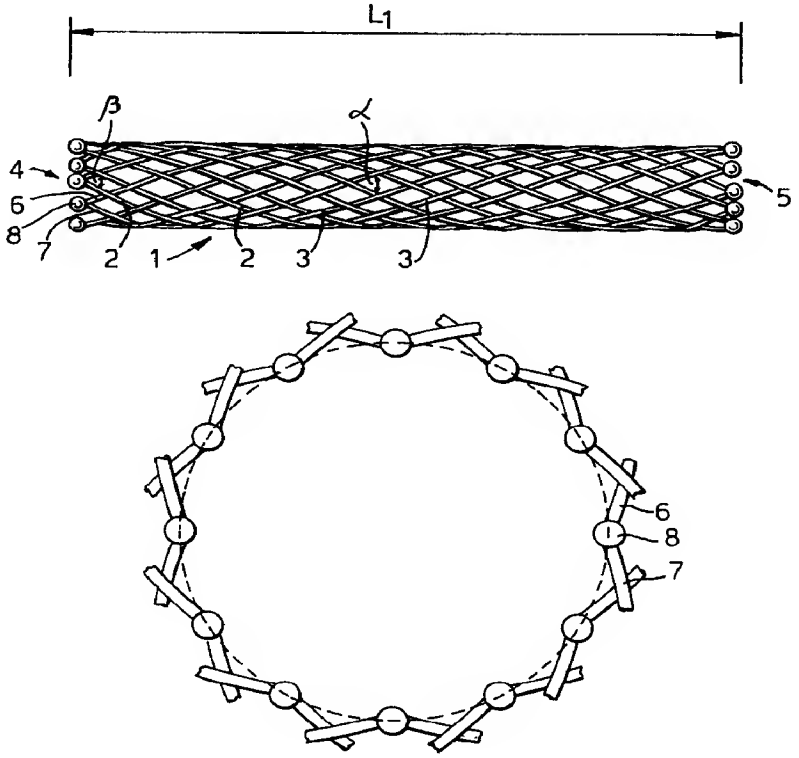
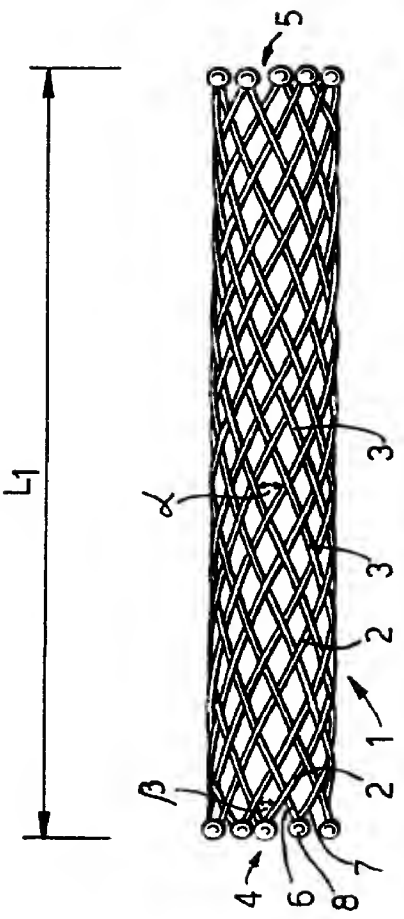


Fig.1.



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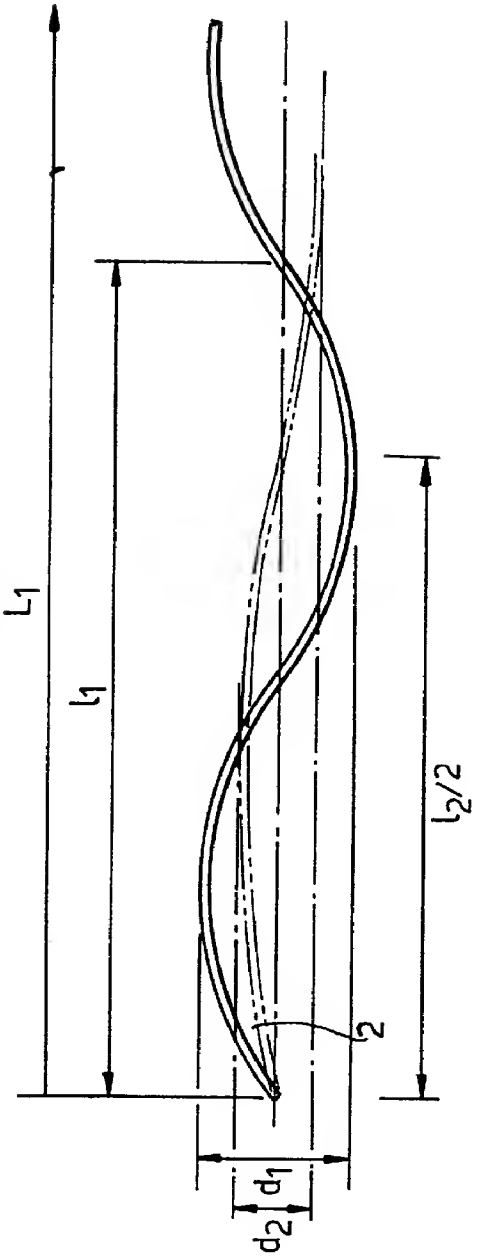


Fig.3.

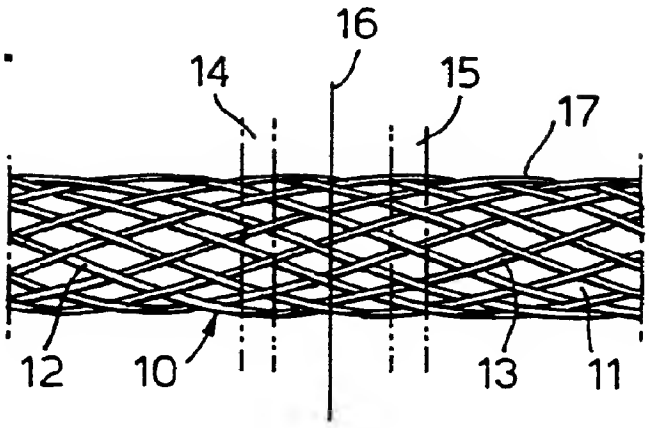


Fig.4.

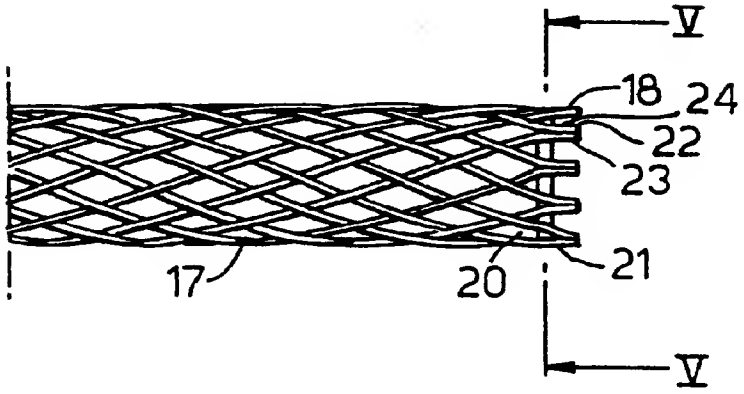


Fig.5.

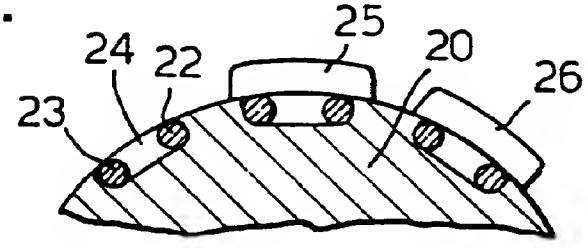


Fig.6.

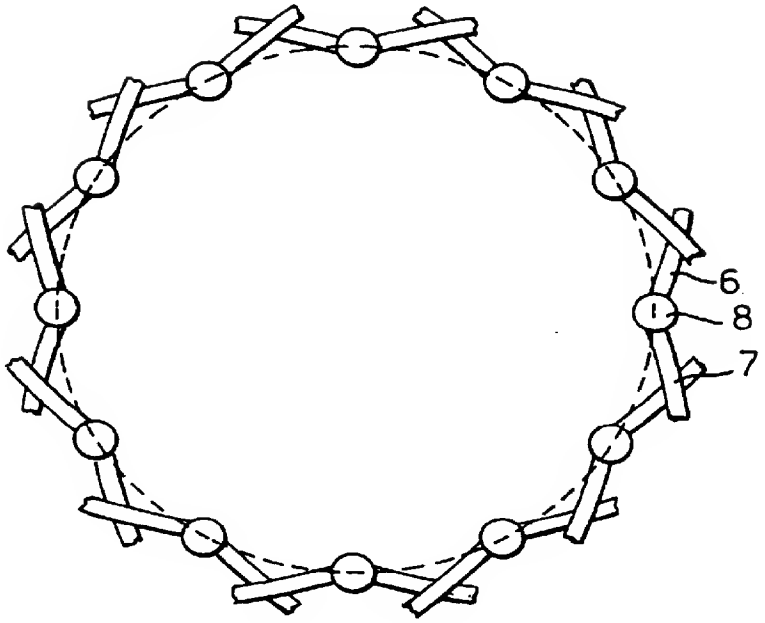


Fig.7.

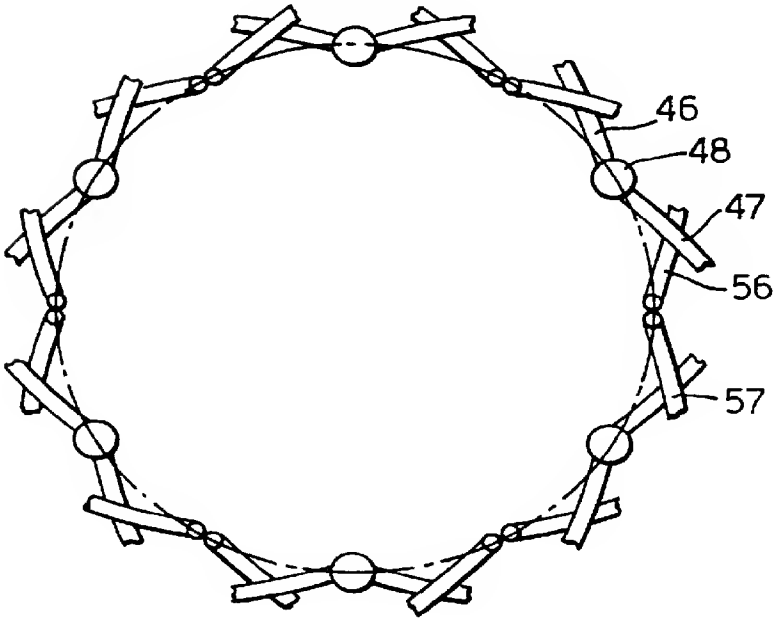


Fig.8.

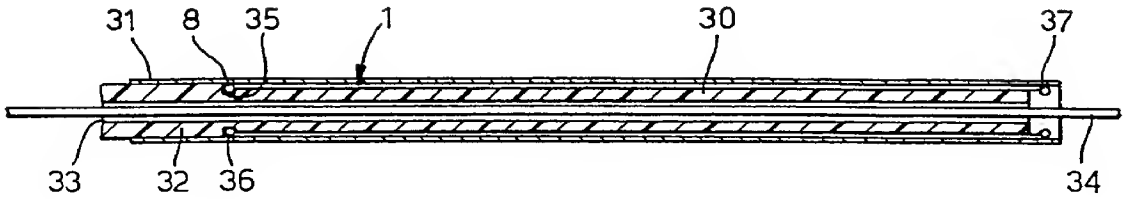


Fig.9.

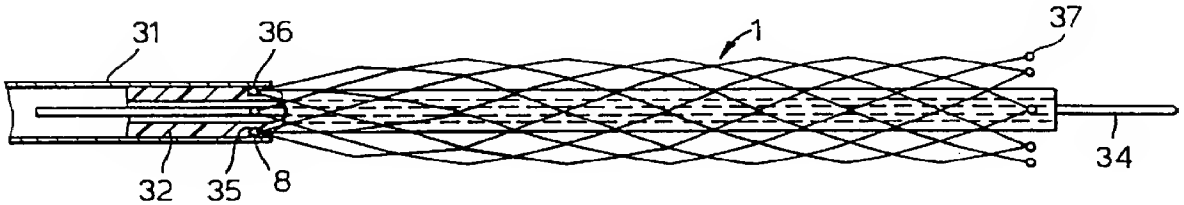
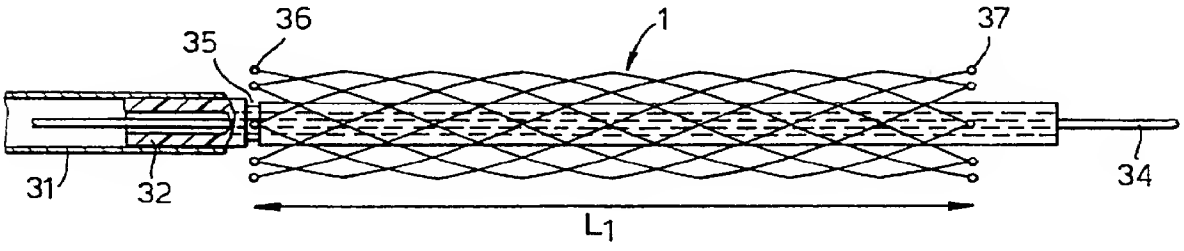


Fig.10.



BRAIDED STENT

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an implantable stent for transluminal implantation in body lumen, especially found in peripheral and coronary blood vessels, but also for use in bile ducts, urethras or ileums.

2. Description of the Related Art

There are several designs of stents, permanently implantable devices, for transluminal insertion into blood vessels and other lumen to prevent or reverse occlusion thereof. There are three basic categories of device, namely heat-expandable devices, balloon-expandable devices and self-expanding devices. The present invention is concerned with self-expanding devices with an optional heat expanding capability, that is which are inserted into the body lumen in a radially compressed condition and which are mechanically biased towards a radially expanded position. Upon being released in the blood vessel at the desired position, the stent expands radially exerting outwardly directed pressure upon the inner surface of the wall of the body lumen in which it is positioned.

One such expanding device which is commercially available is the so-called Wallstent. The device is described in WO-A-83/03752. It consists of two sets of counter-rotating helical filaments of metallic wire which are braided together in a one over/one under pattern. Although it is suggested in the above mentioned patent specification that the axially directed angle α between filaments at crossover points can be acute, it is preferably at least 900 and more preferably 1000 or more, which the author indicates is essential to provide adequate radial strength in use such that the stent remains in its radially expanded condition.

There are difficulties with the braided stent of this type. One difficulty is that with a high angle α the change in axial length between the radially expanded and the radially compressed condition is generally high. One way of overcoming that problem has been described, in WO-A-92/00043, which describes a stent consisting of two co-axial and slidably connected braided stent segments. In the radially compressed condition the stent segments are in a telescoped condition such that the stent portions overlap with one another over a higher proportion of their respective lengths. Upon deployment each segment contracts in the axial direction, such that the length of overlap between the sections is decreased whilst retaining the same distance between the stent ends. This arrangement, however, adds complexity to the manufacture and deployment and it is difficult to allow for the mutual sliding between stent segments without snagging.

Another difficulty with braided stents in general is the tendency of the filaments at the end of the stent to unravel and splay outwards before or after deployment. This tendency makes the stent difficult to handle and the splayed ends can damage the inside wall of the body vessel in which the stent is deployed. In WO-A-83/03752, it is suggested that the filaments may be joined to one another at the end of the stent. However, as explained in a later specification by Wallsten et al in U.S. Pat. No. 5,061,275, for stents with a high angle α between counter-rotating filaments, that this rigidifies the ends of the prosthesis. This makes it difficult to compress the stent into its radially compressed condition. It is also said to accentuate the risk of penetration of the ends of the filaments through the wall of the vessel.

In DE-A-4,240,177 & U.S. Pat. No. 5,503,636, a braided stent is formed from wire having a rectangular cross-section.

The wires are rigidly connected to one another at the crossover points and at the ends of the stent, by sheathing the filaments with a plastics material, applied whilst the stent is held in its radially expanded condition, in which the angle α is obtuse.

An early disclosure of a dilator for body vessels appears in GB-A-1205743. This consists of counter-rotating helices which may be braided or may not be braided but joined at the crossover points. Where the dilator is made from counter rotating wire helices, it is suggested that the ends of the metal wires may be joined by swaging or welding. The angle between filaments at the crossover is said to be preferably in the range 45° to 60°, which is said to give a desired low ratio of axial extension to change in diameter (i.e. length change upon change in radius).

Another example of a braided stent is described in EP-A-0,183,372. The filaments in this publication are formed preferably of plastics material and the device generally has a warp thread extending parallel to the axis of the stent. The warp filament may be formed of shrinkable plastics to allow expansion of the stent insitu to its radially expanded condition.

SUMMARY OF THE INVENTION

A new radially self-expanding stent according to a first aspect of the invention adapted for implantation in a body passage comprises first and second sets of mutually counter-rotating metallic filaments which are braided together and define a tubular stent body having two ends which is mechanically biased towards a first radially expanded configuration in which it is unconstrained by externally applied forces and can be retained in a second radially compressed configuration, in which in the said first configuration the angle α between the filaments at a crossover point at the mid point of the stent is less than 90° and in which some or all of the filaments at the ends of the body are fixed together in pairs each consisting of counter-rotating filaments such that the angle at which the filaments are fixed is within the range $\alpha-10$ to $\alpha+10$ by a bead of metal which has a diameter of at least 1.2 times the mean diameter of an individual filament.

DETAILED DESCRIPTION OF THE INVENTION

Although the ends of the filaments may be fixed together by other means, for instance by swaging as disclosed in GB-A-1,205,743, mentioned above, it is most convenient for the fixing to be by welding. Although the welding can be by resistance welding and/or by pressure, it is preferred for heat to be used, generally by plasma welding. Preferably the welding softens the metal such that it forms a globule before resolidifying to form a bead.

For some embodiments and applications it may be adequate to weld some but not all of the filament ends. For instance it may be convenient to weld every third pair of counter-rotating filaments at the end of one or both ends of the stent body. Preferably at least every other pair is welded at both ends, more preferably every pair at one, or preferably, both ends.

Preferably no filler wire is used in the welding although it may, for some purposes, be useful to include filler wire, for instance where the filler has different, usually greater, radiopacity than the material from which the metal filaments are made. The formation of a bead and/or the use of high radiopacity filler material at the join enables the ends of the stent to be made more radiopaque (to X-rays transmitted

perpendicular to the axis) than the body of the stent between the ends. This assists in visualisation of the stent during an operation.

A bead generally has a diameter of at least 1.2 times that of the diameter of the filament, for instance at least 1.5 times or as much as or more than 2 times the diameter. The diameter of the bead is usually no more than 3, preferably less than 2.5, times the diameter of the filament. We have found that it assists retention of the stent on a delivery device and its delivery from that device if the bead's periphery extends outwardly beyond the periphery of the stent as defined by the filament surfaces, preferably on the inner and outer wall. This results in the bead providing shoulders on either or both the inner and outer walls which can provide an axially directed surface against which a corresponding axially directed surface on a movable component of a delivery device can bear to impose motion of the stent relative to other components of the delivery device. Preferably each bead provides shoulders in forward and rearward axial direction. The shape of the resolidified bead at least on the outer wall of the stent is generally rounded, for instance approximately spherical, and this provides a smooth external stent surface to minimise damage to the inside wall of the vessel in which the stent is implanted.

Where the ends of the filaments are joined together using a treatment involving the use of high temperatures, this may change the properties of the material of the filament in the portion subjected to the increased temperature, generally at the end portions and especially where the filaments are made of steel. Since this may affect the mechanical properties of the wire such that a difference is imposed in properties between the ends and the body between the ends, it may be desirable to anneal the stent before or after the welding, for instance by subjecting the central portion, usually the entire stent, to heat treatment. For instance where the metal from which the filaments are made is a high cobalt stainless steel, welding is generally carried out at the temperature of 1480° C. It is suitable for annealing to be conducted by subjecting the stent after the welding operation to heat treatment at the annealing temperature for the metal for a sufficient period. For high cobalt steel, for instance, the annealing is carried out at a temperature in the range 510 to 530° C., for instance around 520° C. for a period of at least 2 hours, preferably about 3 hours.

The first radially expanded diameter is the diameter adopted by the stent when no externally directed force is exerted upon it, that is when it expands in air. This diameter is somewhat greater than the internal diameter of the lumen into which stent is to be implanted since this results in the stent exerting a continuous outwardly directed force on the internal wall of the body lumen in which it is located. In this fully unloaded conformation the angle α between filaments is less than 90°. Generally it is less than 85°, preferably in the range 65–85°, most preferably in the range 70 to 80°.

Preferably the angle between the filaments at a crossover point at the mid point of the stent in situ when implanted in a body lumen is in the range 60–90°, preferably in the range 65–75°.

Preferably the angle at which the filaments are fixed at the ends of the stent is less than a. The angle is preferably in the range $\alpha-5$ to $\alpha+5$, more preferably $\alpha-5$ to α.

The metallic stent is generally provided with a biocompatible coating, in order to minimise adverse interaction with the walls of the body vessel and/or with the liquid, usually blood, flowing through the vessel. The coating is preferably a polymeric material, which is generally provided by applying to the stent a solution or dispersion of preformed polymer in a solvent and removing the solvent. Non-polymeric coating materials may alternatively be used. Suitable coating materials, for instance polymers, may be polytetrafluoroethylene or silicone rubbers, or polyurethanes which are known to be biocompatible. Preferably however the polymer has zwitterionic pendant groups, generally ammonium phosphate ester groups, for instance phosphoryl choline groups or analogues thereof. Examples of suitable polymers are described in our earlier application number WO-A-93/01221. Particularly suitable polymers described in that specification are those which are cross-linkable after coating, since these remain stably adhered to the surface. We have described other suitable biocompatible coating polymers which may be used in WO-A-94/16748, WO-A-94/16749 and WO-A-93/15775. Polymers as described in those specifications are hemo-compatible as well as generally biocompatible and, in addition, are lubricious. It is important to ensure that the metallic surfaces of the stent are completely coated in order to minimise unfavourable interactions, for instance with blood, which might lead to thrombosis. Although it may be possible to avoid the exposure to blood or metal surfaces at the crossover points, on the mutually contacting portions of the filaments, by sheathing the entire crossover points and hence fixing the filament to one another, as described in DE-A-4,240,177 (mentioned above), it is preferred that the crossover points along the body of the stent should not be fixed to one another but should be allowed to move, for instance slide relative to one another. It is thus preferred for the coating to cover entirely the wires even at the crossover points. This can be achieved by suitable selection of coating conditions, such as coating solution viscosity, coating technique and/or solvent removal step. A preferred technique is described in the worked example set out below.

It is preferred that each filament of the stent should execute at least one full turn of the helix. If the filaments execute less than a full turn, even with the joining of the ends of the filaments, the stent may be relatively unstable. Preferably each filament executes at least 1.2 turns, though generally less than three turns, preferably less than two turns. It is preferred that the stent be formed from at least 4, more preferably at least 8 and most preferably at least 12 filaments in each direction. The number of filaments depends at least in part upon the diameter of each filament as well as the desired diameter and the desired size of the openings between the filaments of the stent in its radially expanded and contracted condition. The number of filaments and their diameter affects the flexibility of the stent in its radially contracted condition during delivery and it is preferred for the stent in that condition to be as flexible as possible. Generally the number of filaments in each direction is less than 32, more preferably from 24 downwards.

The filaments may be made from circular section wire. It may, alternatively be advantageous for rectangular section wire to be used, for instance as described in DE-A-4240177 and in the early Wallsten patent WO-A-83/03752. The use of flat (rectangular section wire) may provide optimum radial strength characteristics whilst minimising the overall thickness of the stent, especially at the crossover points, thereby minimising any interference of the liquid flow in the body passageway. The area of contact between wires at the crossover points is maximised by the use of flat wire which increases the amount of friction between the wires upon relative movement, for instance during any changes in radius. This should increase the resistance of the expanded stent to radial contraction in use although it may be disad-

vantageous to increase this area during delivery. The use of oval wire (with the smaller dimension being arranged substantially radially with respect to the stent axis) may provide a particularly advantageous combination of strength whilst minimising the contact area at crossover points.

The braiding is usually in a one over-one under pattern although other patterns such as one under-two over or two under-two over could be used.

The thickness of the filaments depends upon the desired final diameter (open diameter) of the stent. Wire having a diameter of 0.04 mm upwards, for instance up to 0.20 mm may be used. Wire with diameters at the lower end of the range would generally be used for making stents for use in small blood vessels, for instance in coronary arteries, where the diameters of the stents is generally in the range 0.5 mm up to 4.0 mm (fully radially expanded diameter). Larger stents may be used in peripheral blood vessels, aortic aneurisms or in stents for use in urological passageways, the oesophagus and in the bile duct, where the stent may have a diameter up to about 30 mm.

The length of the stent in the fully unloaded conformation may be in the range 10 to 500 mm. The length depends on the intended application of the stent. For instance in peripheral arteries the stent may have a length at the upper end of the range, for instance in the range 100 to 300 mm. For coronary arteries, the length may be in the range 10 to 50 mm.

For most of the passageways, the diameter of the stents in the first radially expanded conformation is substantially constant along the length of the stent. The stent may flare or have a reduced diameter towards the end portion, in some instances. However, for an insertion into some body passages it is preferred for the diameter, that is the cross-sectional area, to vary along the length of the stent. For instance it may reduce migration of a device by providing it with a varying diameter along its length such that increased diameter sections and/or reduced diameter sections locate at and interact with, respectively, increased diameter body passageways (for instance openings into a higher volume organ) or reduced diameter sections, for instance at a sphincter. Such varying diameter portions may be provided by use of an appropriate braiding mandrel, or alternatively by a post-braiding heat treatment, welding or by provision of shaped restraining means such as non-helical filaments etc. Alternatively two or more stent segments may be fitted together for instance by welding two independently formed sections having the desired shape. One particular application of a varying diameter stent is a stent for use in urological passageways, for instance to overcome benign prostatic hyperplasia.

The filaments from which the braided stents are made are formed of a metal, for instance surgical steel, usually of a type having good elastic properties, for instance a high cobalt stainless steel. These such materials give a stent having good self-expanding capability.

In addition to the self-expanding capability of the stent, it may be provided with a temperature dependent mechanical characteristic which allows a mechanical property of the stent to be changed by heating the stent from a temperature below transition temperature to above transition temperature. Thus some or all of the filaments may be formed from a shape memory alloy material such as nitinol. In such cases, in the stent prior to implantation, the stent is at a temperature below the transition temperature at which the metal changes from the martensitic structure to the austenitic structure. The filaments are adapted such that a transition from below the transition temperature to above the transition temperature will result in the stent either adopting a radially further expanded configuration or, preferably, retaining the same shape but having an increased resistance to radial collapsing under inwardly exerted pressure, due to the greater hardness of the metal at the higher temperature.

According to a further aspect of the invention there is provided a radially self-expanding stent adapted for implantation in a body passage which comprises first and second sets of mutually counter-rotating metallic filaments which are braided and define a generally tubular stent body having two ends which is mechanically biased towards a first radially expanded configuration in which it is unconstrained by externally applied forces and can be retained in a second radially compressed configuration and in which the helically arranged filaments include filaments which are formed of an alloy which can change shape and/or hardness when heated from a temperature below a transition temperature of the alloy to a temperature above the transition temperature, in which the stent is below the transition temperature of the alloy and the shape memory alloy filaments of the stent are adapted to be changeable, when the stent is heated to a temperature higher than the transition temperature, either to a shape where the stent adopts a third maximal radially expanded configuration in which the diameter of the stent is greater than in a said first configuration or to an increased hardness such that the resistance of the stent to radial compression is increased.

The stent of the second aspect of the invention preferably has the features of the stent of the first aspect. This it preferably has welded ends and preferably has an angle α less than 90° in the maximally expanded condition.

The alloy which is used in this aspect of the invention preferably has a transition temperature in the range 30 to 45° C., more preferably around body temperature. It can be heated either by contact with a heater or, where the transition temperature is about 35 to 40° C., by being implanted in the patient where it will warm up from room temperature to body temperature, i.e. to the transition temperature. Such alloys are known. Where such an alloy is used it may be used to form all or only some of the filaments of the stent. Where the filaments of such an alloy are used and are desired to be welded, a counter-rotating pair of filaments of the same material are preferably welded together. Where there are pairs of one type of metal to be welded and pairs of another type of metal to be welded, the welding may be carried out in two stages, especially where the optimum welding conditions for the materials are different.

When it is used, the stent of the second aspect of the invention is inserted into the body lumen in its radially compressed configuration and is allowed to self-expand within the vessel. Subsequently the stent is heated to a temperature above a transition temperature of the alloy thereby causing the stent to assume a radially further expanded configuration and/or exert a greater outwardly directed force on the internal wall of the body lumen and/or resist radial compression to a greater degree. The invention thus provides an added degree of control as compared to a standard self-expanding stent upon the radial strength of the stent and/or the pressure it exerts on the vessel wall.

According to the invention there is also provided a method of making the new stents by braiding filaments over a first mandrel to make an elongate precursor, severing a pre-selected length from the precursor, placing the severed portion onto a second mandrel which has a diameter which is within the range (0.8 to 1.25)×d (where d is the diameter

of the stent in its radially expanded condition) such that one end of the braided portion extends beyond the end of the second mandrel and in the method the protruding ends of at least some of the filaments are joined to each other in counter-rotating pairs, whereby each pair of joined counter-rotating filaments is joined by a bead of metal having a diameter of at least 1.2 times the mean diameter of the individual filaments.

The braiding is carried out on a standard braiding rig which generally provides a continuous length of braided tubing. The filaments are wound on to the bobbins and the process conditions, for instance in terms of the tension in the filaments, the diameter of the bobbin and the braiding angle during the braiding process determined by the haul off speed are selected using common general knowledge of the person skilled in the art of braiding, to produce a product having the desired characteristics in terms of expandability, radial strength and angle. It has been found that increasing the tension in the filaments during the braiding step, for instance to close to a maximum value above which the filaments would break, provides a stent having good radial strength and which does not collapse upon axial bending of the stent.

After the braid has been formed, it is subjected to any heat treatment and to welding. Whilst these steps may be carried out in either order, it may be convenient to subject an elongate stent precursor, which will be used to form a number of stents, to heat treatment prior to welding, which involves cutting the elongate precursor into stent length sections. It is preferred for heat treatment to be carried out in an inert gas environment for instance of argon gas.

The stent could also be included in a graft used to replace damaged blood vessels (aneurisms). For instance a stent according to the invention could be surrounded by a sleeve, of a porous or non-porous, elastic or inelastic, material. Alternatively a sleeve could include one stent at each end, secured for instance by suturing or other means, to the stent. The stent can be sterilised before use using standard techniques.

The joining step of the process is generally by welding the ends together, preferably by using a filler-free technique. As mentioned above, the welding generally creates a globule of molten metal which resolidifies to form the bead. It is most convenient for all the filaments which are required to be welded at one end of the stent to be joined in their respective pairs simultaneously and, in a separate step, for all the filaments which are required to be welded at the other end of the stent to be joined in their respective pairs simultaneously.

Where the ends of the filaments are joined by welding, this generally means that the filaments in the region of the stent adjacent to each end have been subjected to a higher temperature than the filaments in the body of the stent between the two ends. This can result in a change in the hardness of the metal adjacent the ends of the stent which may be undesirable. It may be advantageous, therefore, to subject the entire stent to an annealing step such that the hardness of the metal throughout the stent is equalised. Annealing is, for instance, carried out by subjecting the previously unheated section of the stent or, more usually, the entire stent, to heat treatment at the annealing temperature. For high cobalt steel, for instance the annealing temperature is in the range 510 to 530, preferably around 600° C., for a period in the range 1 hour to 1 day usually at least 2 hours preferably in the range 3 to 4 hours. This annealing step does not generally further change the hardness of the end section. Alternatively the stent precursor can be annealed prior to the end joining step.

The elongate precursor is generally sufficiently long for it to be used to make several stents, for instance at least five. Portions of an appropriate length are severed from the elongate precursor, generally after securing the ends to prevent them immediately unravelling upon severance. For instance it is possible to weld the filaments at crossover points near to the end of the portion prior to severance, for instance by resistance welding in a ring around the precursor, generally at two positions, one on each side of the place where the precursor is to be severed.

The second mandrel on which the severed length of braided portion is mounted is generally specifically adapted for carrying out the step of joining the filament ends together. Generally it is provided with circumferentially arranged pockets at its end, in each of which-sits a pair of filaments to be joined together. The width of the pocket and its shape allows selection of an appropriate angle at which the filaments are to be joined. The length of filaments extending beyond the end of the mandrel generally affects the shape and size of the globule formed upon carrying out the welding step. It is preferred for a heat sink to be contacted with the filaments, for instance the mandrel itself or a ring of material provided outside the filaments around the ends of the mandrel. This heat sink also affects the shape and position of the bead of metal formed upon carrying out the welding step.

Where the final stent is to be coated with a biocompatible polymer, this coating is carried out at a final step, after the welding and any heat annealing. Preferably the entire stent is immersed in a coating liquid and is then drained. Subsequently the coating is dried to leave an adherent polymer coating. Usually the coating liquid is a solution or dispersion of polymer in a solvent and, in the drying step, solvent is removed by evaporation. As mentioned above, it is important for all surfaces of the filaments to be coated, including the surfaces which contact one another at the crossover points. In a preferred coating step of the invention, as a part of the drying step, an axially directed flow of gas is passed along the stent to which coating solution has been applied. This gas causes the solution to flow between the filaments at the crossover points, so as to provide an overall coating.

The stent can be delivered using conventional delivery devices for self-expanding stents generally by percutaneous transluminal techniques. The stent may be delivered from a delivery device comprising a pusher and an external sleeve. The stent is retained against the end of the pusher within the sleeve, so that the device can be inserted transluminally until the stent is in the desired location in the body passageway. The pusher can then be used to push the stent so that it moves distally relative to the sleeve and is extruded therefrom to be positioned in the body passageway at the desired location. Such devices are described, for instance, in U.S. Pat. No. 4,655,771 (Wallsten). In such a delivery device, the stent is held in its radially compressed configuration by being retained within the sleeve. It expands to its radially expanded configuration as it is extruded from the end of the sleeve.

An alternative delivery device is also described in U.S. Pat. No. 4,655,771, which is similar to the device described in GB-A1205743, in which the stent is held at each end such that the ends are pulled apart, thereby stretching the length axially and reducing the diameter. The stent can be delivered by moving the ends together and releasing them. This allows central deployment, that is deployment in which the central section of the stent expands whilst the ends are retained in the radially compressed configuration. This may allow the stent to be moved within the body passageway during

deployment in both directions until the desired location is achieved. This is an improvement as compared to the device extruded from one end of a sleeve, which can be moved in one direction only during deployment.

A further device for deploying a self-expanding stent is described in EP-A-0408245. In this device means are provided for allowing the stent to be retracted back onto an external sleeve by providing an internal pusher which have a shoulder beyond the distal end of the stent with a proximally directed shoulder which bears against the distal end of the stent allowing the stent to be pushed back into the sleeve prior to complete delivery.

A further device for delivering a self-expanded stent has been described in U.S. Pat. No. 5,078,720. In this device the stent is retained in an annular space having a proximally directed opening and which is fixed to the end of a pusher. The stent can be positioned in a retrograde manner, that is released from the proximal end first, by moving the device having the annular space distally whilst providing relative movement of the stent by providing a proximally direct shoulder on an inner tube which moves relative to the device having the annular space. A centrally deploying device is described also in U.S. Pat. No. 5,201,757. In this device, each end section of the stent is retain within an annular space, with the compressed diameter being achieved by retention within the annular space, the stent bearing against the external wall of the space.

Wallsten has described an alternative device referred to as the "rolling membrane device", in which a membrane is folded over upon itself to provide a double wall sleeve within which the stent is retained. When the outer wall is moved proximally, the distal fold travels proximally, exposing the stent allowing radial expansion from the distal end.

U.S. Pat. No. 5,415,664 describes a method for retrograde delivery of a self-expanding stent.

The provision of a stent having welded ends, in which the beads by which the ends are welded have peripheries extending beyond the periphery defined generally by the filaments allows for a particularly convenient delivery device and method, as described herein below. The present invention includes apparatus comprising a combination of delivery device with stent mounted ready for delivery.

In a preferred aspect of the invention there is provided a combination of stent in its radially compressed configuration and delivery device in which the delivery device comprises an internal pusher tube comprising an inner guidewire lumen for receiving a guidewire, and an external sleeve, the sleeve and pusher defining there between an annular space, wherein the stent is surrounded along substantially its entire axial length by the sleeve and at least one end of the stent is retained in the annular space between the sleeve and pusher. The device comprises means for providing relative axial movement between the pusher and the sleeve, preferably such that the sleeve moves proximally (with respect to a component of the device held in an axially fixed position by the surgeon) whilst the pusher moves distally to an extent whereby the stent is extruded beyond the distal end of the sleeve for delivery.

Where the stent comprises beads which provide a shoulder, as defined above, the pusher is provided with corresponding axially directed surfaces which can cooperate with these shoulders to impose motion on the stent relative to the sleeve. These surfaces are generally provided as the walls of a circumferential groove in the outer wall of the pusher tube, the groove being of a suitable width and/or depth for receiving the beads. Alternatively the stent may be delivered from a device in which the sleeve and pusher provide differential levels of friction with the stent whereby when the sleeve and pusher are moved relative to one another, the stent stays substantially fixed relative to the components (usually the pusher) and slides relative to the other.

The delivery device may have means to allow central deployment of the stent, that is allowing for radial expansion of the stent in the central portion prior to release of the ends from the radially compressed state on the delivery device. Central deployment may be achieved by means as described in some of the above mentioned prior art specifications (as indicated).

Where the stent is deployed centrally, it is possible for the position of the stent to be readjusted prior to full deployment or alternatively to be removed from the vessel altogether. Where the distal end of the stent is released, only proximal readjustment of the stent is possible when the stent is partially deployed, otherwise the end could become embedded in the vessel wall and cause damage. Likewise, where the proximal end is fully delivered prior to the distal end, the position of the stent can be readjusted in a distal direction but not a proximal direction. The delivery device may allow for the stent to be retracted back into a sleeve after partial deployment, to allow for respositioning.

The present invention is illustrated further in the accompanying figures in which:

FIG. **1** is a side view of a stent according to the present invention in relaxed, radially expanded condition;

FIG. **2** shows the minimum path of one filament in the stent of a first aspect of the invention;

FIG. **3** shows a plan view of a portion of the first mandrel carrying a stent precursor during the execution of the method of the present invention;

FIG. **4** shows in plan a portion of the second mandrel carrying a stent portion prior to joining of the filaments to one another;

FIG. **5** is a partial section along line V—V of FIG. **4**;

FIG. **6** is a partial end on view of another embodiment of a stent showing every pair of counter-rotating filaments welded;

FIG. **7** is a partial end on view of an alternative stent to that of FIG. **6**, in which every alternate pair of counter-rotating filaments is welded.

FIG. **8** is a section on an axial plane of a stent loaded in a delivery device in its radially compressed conformation;

FIG. **9** shows the system of FIG. **8** with the stent partially deployed;

FIG. **10** shows the system of FIG. **8** with the stent fully deployed.

As shown in FIG. **1**, a stent **1** is formed of ten wire filaments **2** arranged in right handed helices and ten filaments **3** arranged in left handed helices. The filaments are braided in a one over/one under pattern. The angle α between the filaments in the radially expanded (relaxed, unloaded) condition is generally in the range 60–90, in this embodiment in the range 68–72°. Each filament, as shown more clearly in FIG. **2** which is enlarged relative to FIG. **1** executes just over one complete turn (about 1¼ turns) within the length L of the stent. Each turn of the helix has a pitch of l_1. The diameter of the stent, and of each helix is d_1. In the radially compressed condition and axially extended condition, the length L increases to L_2, whilst the pitch of each helix increases from l_1 to l_2 and the diameter reduces from d_1 to d_2. The dotted line in FIG. **2** shows a portion of

the filament **2** in its radially compressed state and indicates the length of one half of a turn of the helix as $l_2/2$.

Reverting to FIG. **1**, at the ends **4** and **5** of the stent a pair of counter-rotating helices **6**, **7** are connected together by an approximately spherical bead of metal **8** formed by fusing the wires **6** and **7**. The angle β on the tangential plane on the surface of the body between the filaments **6** and **7** is, in this embodiment, slightly lower than the angle α by about 5°. Alternatively it may be higher than or about the same as the angle α. With the angle β selected as illustrated, in the fully unloaded condition, the ends of the stent do not flare, or do not flare to a disadvantageous degree.

The stent illustrated in FIG. **1** is, for instance, suitable for implanting in a coronary artery. The diameter d_1 is in the range 2.5–4.0 mm. The diameter d_2 of the stent, in its axially compressed condition is generally at least ⅓ less than diameter d_1, and for instance in the range 0.5 to 2.0 mm. The wire used to form the filaments has a circular section and a diameter of 0.09 mm. The wire is formed from a high cobalt stainless steel. The beads **8** include no filler material but consist only of the material from which the wire of the filaments is formed. The blobs generally have a diameter in the range 0.18 to 0.22 mm. When visualised using X-rays, the end portions of the stent including the beads **8** have an increased radiopacity compared to the body of the stent, for instance by a factor of at least about 4.

The length of the stent in this condition is L_2 (not shown), whilst its diameter is d_2. The angle α_2 between the filaments is reduced by 10 to 60% of the original angle. The stent can be retained in this condition either by exerting radial inwardly directed forces from the stent along its length, or by exerting axially outwardly directed forces at the ends of the stent. The fixing of the ends of the filaments according to the present invention render this latter means of retaining the -stent in its radially compressed condition more convenient since it can be achieved by extending pins or other means between the filaments adjacent to the bead **8**, or beyond the first crossover points along the length of the stent, at each end and increasing the separation between the ends to extend to the stent in the axial direction.

As well as making it convenient to extend the stent, and stabilise it against flaring at the ends, the joining of the ends of the filaments allows the stent further to be axially compressed by exerting axially inwardly directed pressure against each end, so as to expand the radius of the stent, especially in its central portion, beyond the diameter d_1. The stent can thus be used to exert radially outwardly forces at a greater radial distance from the axis (than d_1) inside the blood vessel, for instance adding to or replacing the step of balloon dilatation prior to stent deployment. Without the joining of the filament ends such a step might be completely impossible and, even if it were, the stent ends would be damaged during such an operation. With the angle α being less than 90°, the use of the stent as a dilation device is convenient since a relatively large increase in diameter can be achieved with a relatively small axial reduction in length (as compared to a stent with a higher value of α).

FIGS. **3** to **5** show how some of the steps of the method of the invention are carried out. In FIG. **3**, a portion of a stent precursor which has been formed by braiding ten right handed helical filaments **12** and ten left handed helical filaments **13** all formed of high cobalt steel onto a mandrel **11**. The filaments are again braided in a one over/one under pattern, by the following steps:

1. Wind the material from the supply spools onto the braiding bobbins.
2. Load the bobbins onto the braiding machine taking care to thread the tensioning system correctly.
3. Select the correct size of braiding mandrel (Dependant on the require stent size, usually 2 mm below the required diameter of stent i.e. for a 8 mm diameter stent use 6 mm mandrel).
4. Check the tension of each carrier and ensure that all carriers are of the same tension.
5. Secure all the ends of the wires onto the braid mandrel.
6. Set the haul off speed to obtain the correct braid angle.
7. Operate the machine to produce the desired amount of braid.
8. Secure the leading end of the braid onto the braiding mandrel using adhesive tape.
9. Slide a heat-treatment tube over the braid.
10. Trim a length of braid from around the heat-treatment mandrel allowing the braid to expand into the tube.
11. Remove the tube from braid mandrel making sure that the braid is secured on the inside of the tube.
12. Place both the tube and the braid into the shield box, taking care not to dislodge the braid from the inside of the tube.
13. Seal the box and purge using argon gas for a period of about 30 minutes.
14. Ensure that the oven is at 520° C.
15. Place the shield box into the oven whilst continuing to purge with argon although at a lower flow rate.
16. Monitor the temperature within the shield box via the data logger.
17. Once the internal temperature of the shield box has reached 520° C. allow the samples to dwell for a period of 3 hours.
18. After the 3 hours remove the shield box and allow to cool in air at ambient temperature.
19. Once cooled remove the tubes from the shield box and then remove the braid from the tubes.
20. Place the stent into the welding jig, trim the stent to the desired length before welding the ends.

A resistance welding technique with the welding device arranged in a ring around the stent precursor is used. This retains the filaments fixed relative to one another at these crossover points. Once secured, the wires are severed around the circumference at position **16**, which is located midway between two series of crossover points. With the filaments secured at **15** and, though not shown, at the other, leading end of the stent portion **17**, this can be removed from the mandrel **11**.

As shown in FIG. **4**, stent portion **17** is mounted onto a second mandrel **20** such that the ends **18** of the filaments extend beyond the end **21** of the mandrel. A pair of filaments **22**, **23** is received in a pocket **24** formed in the surface at the end of the mandrel **20**. As shown more clearly in FIG. **5** which is an expanded partial crosssection along line V—V of FIG. **4**, the filaments **22** and **23** are positioned along the edges of the pocket **24** formed in the end of the mandrel **20**.

Also shown in FIG. **5** are two components **25**, **26** of a ring of heat sink components which are positioned across the filaments in the pockets and serve both to hold the filaments stationary and to conduct heat away from the filaments during the welding operation. The heat sink components are generally formed of copper. During the welding step, a plasma welding torch is directed at the ends **18** of the filaments extending beyond the end **21** of the mandrel shown in FIG. **4**. The torch is directed at the ends for a time sufficient to fuse the metal of the filaments such that a globule of metal is formed. The heat sink components **25**, **26** conduct heat away and, when the heat source is removed, the globules fuse to form metal beads **8** shown in FIG. **1**.

During the welding step the filaments near to the beads **8** have been subjected to relatively high temperatures and, where the metal is high cobalt stainless steel, this affects the hardness of the material in the end portions of the stent. This differential hardness between the ends and the central portion of the stent may be disadvantageous and so the stent is annealed after the welding step and before removal from the mandrel **20** by heating at a temperature of 520° C. for 3–4 hours.

After the annealing step, the stent is coated with a solution of a 1:2 (mole) copolymer of (methacryloyloxy ethyl)-2-(trimethylammonium ethyl) phosphate inner salt with lauryl methacrylate in ethanol (as described in example 2 of WO-A-93/01221) as follows. The stent in relaxed form is placed in a tube having a slightly larger diameter than the stent. The tube is filled with coating solution and the solution is allowed to drain steadily from the tube to form a completely coated stent. Immediately thereafter a stream of warm air or nitrogen is directed through the tube at a linear velocity of 0.1–5 m/s at room temperature to 50° C. for a period of 30 seconds to 5 minutes to dry the coating by evaporation of the ethanol solvent.

Examination of the coating by scanning electron microscopy indicated that the coating substantially completely covered all the filaments, including the surfaces of the wires at the crossover points.

An alternative, cross-linkable coating consists of a polymer of 23 mole % (methacryloyloxy ethyl)-2-(trimethylammonium ethyl) phosphate inner salt, 47 mole % lauryl methacrylate, 5 mole % γtrimethoxysilylpropyl methacrylate and 25 mole % of γhydroxypropyl methacrylate. This is applied to the stent by the above described technique from a 5 mg/ml ethanolic solution. The solution is dried as described above and then cured by heating at 70 to 75° C. for a period of at least about 1 hour, for instance overnight. This curing results in substantially complete reaction of the methoxy silyl groups, either with other methoxysilyl groups or with hydroxy groups derived from the hydroxypropyl methacrylate monomer, driving off methanol. The coating, when observed by scanning electron microscope provides complete coverage of the filaments, no bridging at crossover points and is more resistant to damage at the crossover points than the above described two component copolymer.

The coated stent was sterilised by ethylene oxide, gamma radiation or electron beam and was subsequently mounted onto a standard delivery device as is used to deliver a Wallstent ready for deployment. The stent may alternatively be mounted onto the device on the distal end of which is illustrated in FIGS. **8** to **10**.

FIG. **6** shows an end on view of a further embodiment of the stent of the first aspect of the invention. This differs from the stent of FIGS. **1** to **5** since it consists of 12 filaments in each direction. The stent has been made by the same technique as described for FIG. **1** to **4**. Thus each pair **6**, **7** of counter-rotating filaments is welded together at a bead **8**. FIG. **7** shows an alternative embodiment in which every alternate pair is welded. Thus counter-rotating filaments **46** and **47** are welded together at a bead **48**, whilst counter-rotating helices **56** and **57** are not welded together. For some embodiments this gives adequate stability and allows convenient delivery means to be used whilst allowing control of mechanical characteristics by subjecting only half the filaments to the high welding temperatures.

As shown in FIG. **8**, a stent **1** is retained in an annular space **30** between an external sleeve **31** and a pusher tube **32**. The pusher tube **32** has a guidewire lumen **33** allowing passage therethrough of a guidewire **34**. The pusher tube **32** has a circumferential groove **35** in its external wall having a depth and width (in the axial direction) of appropriate diameter for receipt of the beads **8** of the stent at its proximal end **36**. The outer diameter of the pusher tube **32** distal from the groove **35** is preferably less than the outer diameter of the pusher tube proximal from the groove which in turn is dimensioned to allow a snug, sliding fit between the pusher tube and the outer sleeve **31**. The reduced diameter portion distal from the groove **35** allows formation of the annular space **30** between the pusher tube **32** and the outer sleeve **31**.

FIG. **9** shows the stent **1** partially deployed. The pusher tube **32** has been moved distally whilst the outer sleeve **31** has been moved axially in a proximal direction so that the sleeve has been retracted first from the distal end **37** from the stent until, as shown in FIG. **10**, the proximal end of the stent is released from the groove **35**. When the stent is partially deployed as shown in FIG. **9**, it can be retracted into the delivery device by pulling pusher **32** back into the sleeve. Since the beads **8** at the proximal end **36** of the stent are fixed in groove **35** of the pusher, and since the distal wall of groove **35** bears against the shoulder provided by the distal edge of beads **8**, the stent will be retracted back into the sleeve. The retraction may be partial, to make axial repositioning in a proximal direction less damaging on the internal wall of a vessel in which the stent is deployed. Alternatively the stent may be fully retracted to the position shown in FIG. **8** for complete removal from the vessel or repositioning.

As shown in FIG. **10**, the stent is in its fully radially expanded configuration. The guidewire **34** remains in place. It can be seen that the length L_1 of the stent in the radially expanded configuration is less than the length in the radially compressed configuration shown in FIG. **8**. A compensation mechanism could be provided whereby the distal end **37** of the stent remains in the same axial position in the vessel as the rest of the stent is deployed. The stent will not move axially relative to the vessel wall, thereby minimising damage during deployment.

Subsequently the pusher tube **32** will be pulled back to the sleeve **31** for retraction of the entire device along the guidewire and out of the patient.

Optionally after deployment of the self-expanding stent in a body vessel, it may be pushed against the internal vessel wall by a balloon catheter introduced via the guidewire until it is located within the stent. Alternatively, where the stent of the second aspect of the invention is used, the mechanically radially expanded stent which is formed of a shape memory alloy which changes shape or increases in hardness above a transition temperature, it may be desirable to provide means for heating the device to a temperature above the transition temperature of the alloy, where that temperature is above 37° C. For instance a balloon catheter provided with means for circulating heated fluid into the balloon is known and could be used.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

What is claimed is:

1. A radially self-expanding stent adapted for implantation in a body passage comprises first and second sets of mutually counter-rotating metallic filaments which are braided together and define a tubular stent body having two ends which is biased towards a first radially expanded configuration in which it is unconstrained by external applied forces and can be retained in a second radially compressed configuration, in which in the said first configuration the

angle α between the filaments at a crossover point at the mid point of the stent is less than 90° and in which some or all of the filaments at the ends of the body are fixed together in pairs each consisting of counter-rotating filaments such that the angle at which the filaments are fixed is within the range α−10 to α+10, and in which the filaments are joined at a bead which has a diameter of at least 1.2 times the diameter of the filament.

2. The stent according to claim **1** wherein α is in the range of 60° to 90°.

3. The stent according to claim **2** wherein the angle at which the filament ends are fixed is in the range of α−5 to α.

4. The stent according to claim **1**, further comprising a polymeric biocompatible coating comprising a zwitterionic pendant group coating the surfaces of the filaments.

5. The stent according to claim **1**, wherein the filaments are free to slide over each other at the crossover points.

6. The stent according to claim **1**, wherein each beed has a diameter of more than twice the mean diameter of each filament.

7. The stent according to claim **1**, wherein the filaments are formed of a shape memory alloy having a transition temperature and in which the stent adopts the said first radially expanded configuration below the transition temperature of the alloy and, when the stent is subjected to a temperature above the transition temperature of the alloy the stent adopts a maximally radially expanded configuration in which one or both of the diameter and resistance of the stent to radial compression is increased.

8. A method of making a stent according to claim **1**, which comprises braiding filaments over a first mandrel to make an elongate precursor, severing a pre-selected length from the precursor, placing the severed portion onto a second mandrel which has a diameter which is within the range (0.8 to 1.25)×d (where d is the diameter of the stent in its radially expanded condition) such that one end of the braided portion extends beyond the end of the second mandrel and in the method the protruding ends of at least some of the filaments are joined to each other in counter-rotating pairs whereby each pair of counter-rotating filaments is joined by a beed of metal having a diameter of at least 1.2 times the mean diameter of the individual filaments.

9. The method according to claim **8**, which comprises joining the filament ends together by welding.

10. The method according to claim **9**, which comprises annealing the stent before or after the welding step.

11. The method according to claim **8**, which comprises joining all the filaments required to be welded at one end of the stent in their respective pairs simultaneously and, in a separate step, joining all the filaments required to be welded at the other end in their respective pairs.

12. The method according to claim **8**, which comprises subsequently coating the stent with a liquid coating composition and drying the coating to form an adherent coating of a biocompatible polymer.

13. The method according to claim **12**, wherein the polymer comprises zwitterionic pendant groups.

14. The method according to claim **12**, which comprises drying the coating by directing a flow of gas through the stent in an axial direction.

15. A graft comprising at least one stent according to claim **1** surrounded by a sleeve formed of an elastomeric material.

16. A combination of a stent according to claim **1**, the stent being in the radially compressed configuration, and a delivery device, in which the delivery device comprises an internal pusher tube comprising an inner guidewire lumen for receiving a guidewire, and an external sleeve, the sleeve and pusher defining there between an annular space, wherein the stent is surrounded along substantially its entire axial length by the sleeve and at least one end of the stent is retained in the annular space between the sleeve and pusher.

17. The stent according to claim **1**, wherein α is in the range of 65° to 85°.

18. The stent according to claim **1**, wherein α is in the range of 70° to 80°.

19. The stent according to claim **4**, wherein the polymeric biocompatible coating comprises an ammonium phosphate ester group.

* * * * *

EVIDENCE APPENDIX

EXHIBIT B

United States Patent [19]

Ecer et al.

[11] **Patent Number: 4,486,247**

[45] **Date of Patent: Dec. 4, 1984**

[54] **WEAR RESISTANT STEEL ARTICLES WITH CARBON, OXYGEN AND NITROGEN IMPLANTED IN THE SURFACE THEREOF**

[75] Inventors: **Gunes M. Ecer**, Irvine, Calif.; **Susan Wood**, Pittsburgh; **Jan J. Schreurs**, Plum Boro, both of Pa.

[73] Assignee: **Westinghouse Electric Corp.**, Pittsburgh, Pa.

[21] Appl. No.: **390,716**

[22] Filed: **Jun. 21, 1982**

[51] **Int. Cl.**[3] **C23C 15/00**

[52] **U.S. Cl.** ..... **148/31.5**; 148/39; 204/192 N; 427/38

[58] **Field of Search** ..... 148/4, 31.5, 16.6, 39, 148/6.35, 15.5; 204/192 N; 427/38

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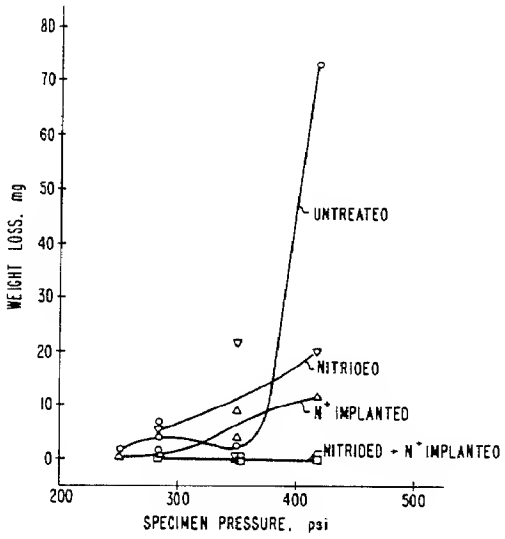
Primary Examiner—L. Dewayne Rutledge
Assistant Examiner—Robert L. McDowell
Attorney, Agent, or Firm—John J. Prizzi

[57] **ABSTRACT**

The present invention pertains to steel articles having improved wear and friction properties and the method of producing these articles. A steel surface containing relatively high levels of nitrogen and having a surface film containing carbon is implanted with high energy ions. Overlapping layers enriched in carbon and nitrogen are formed beneath the surface and provide the steel with a surface that has improved wear and friction characteristics.

10 Claims, 5 Drawing Figures



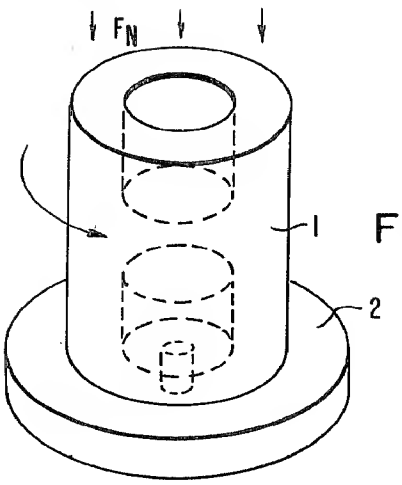

F_N
1
2

FIG. 1

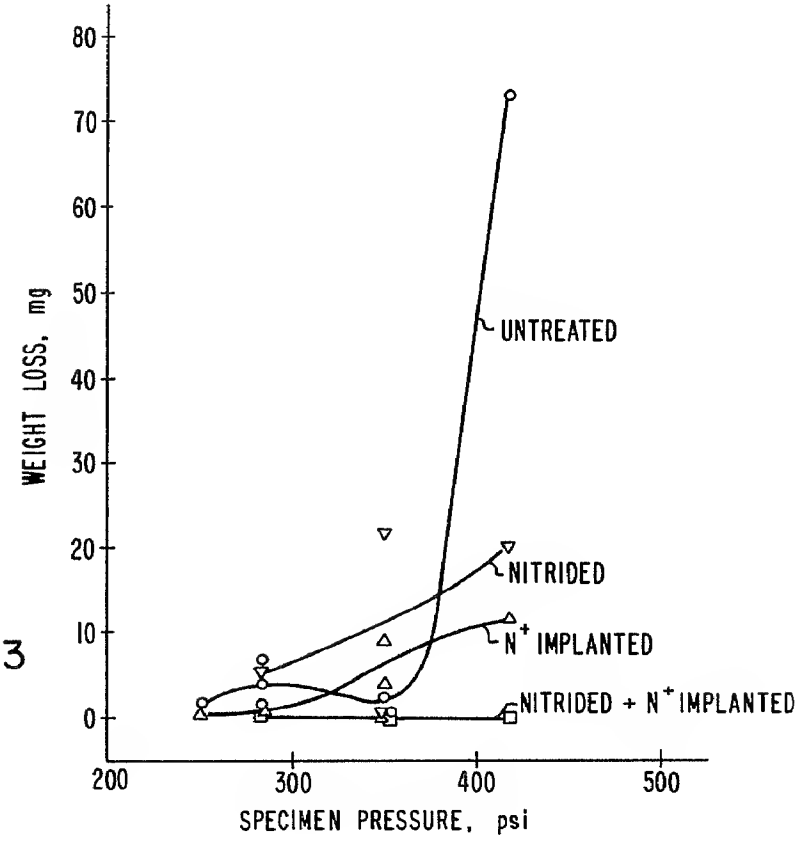
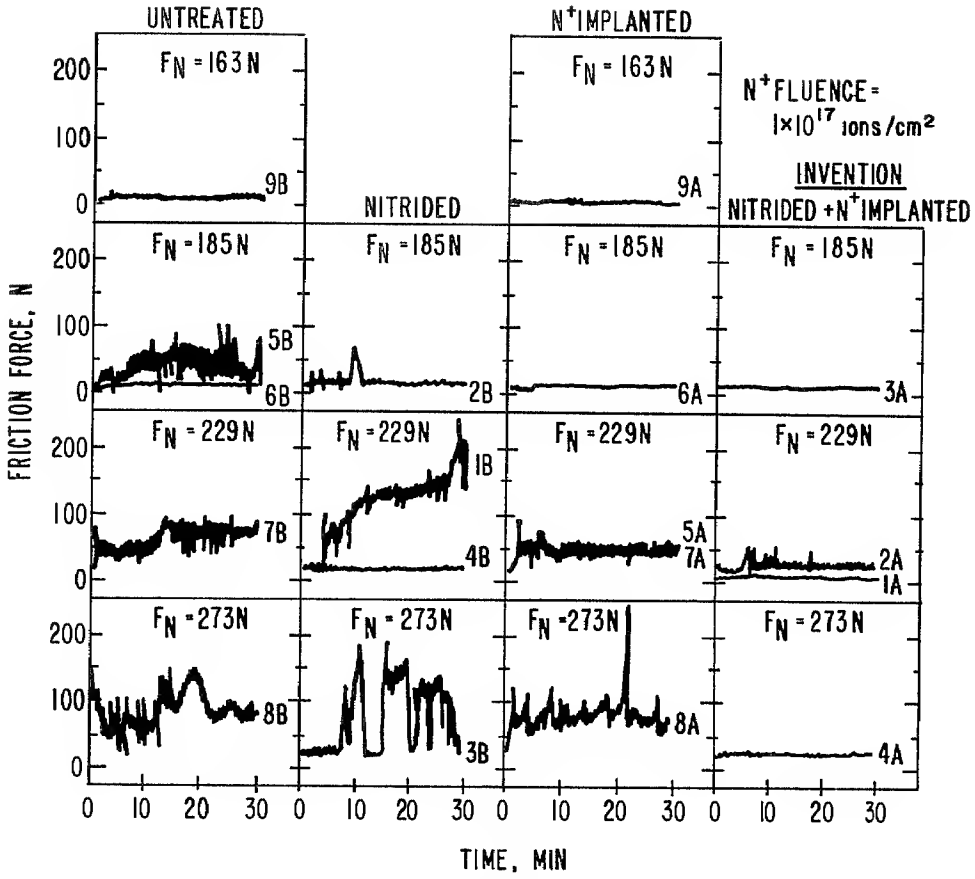

WEIGHT LOSS, mg
80
70
60
50
40
30
20
10
0
200
300
400
500
SPECIMEN PRESSURE, psi
UNTREATED
NITRIDED
N+ IMPLANTED
NITRIDED + N+ IMPLANTED

FIG. 3


UNTREATED
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N+IMPLANTED
N+FLUENCE = 1×10^17 ions/cm²
INVENTION
NITRIDED +N+IMPLANTED
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FN = 185N
FN = 229N
FN = 273N
FRICTION FORCE, N
TIME, MIN
0
10
20
30
100
200
9B
9A
5B
6B
2B
6A
3A
7B
1B
4B
5A
7A
2A
1A
8B
3B
8A
4A

FIG. 2

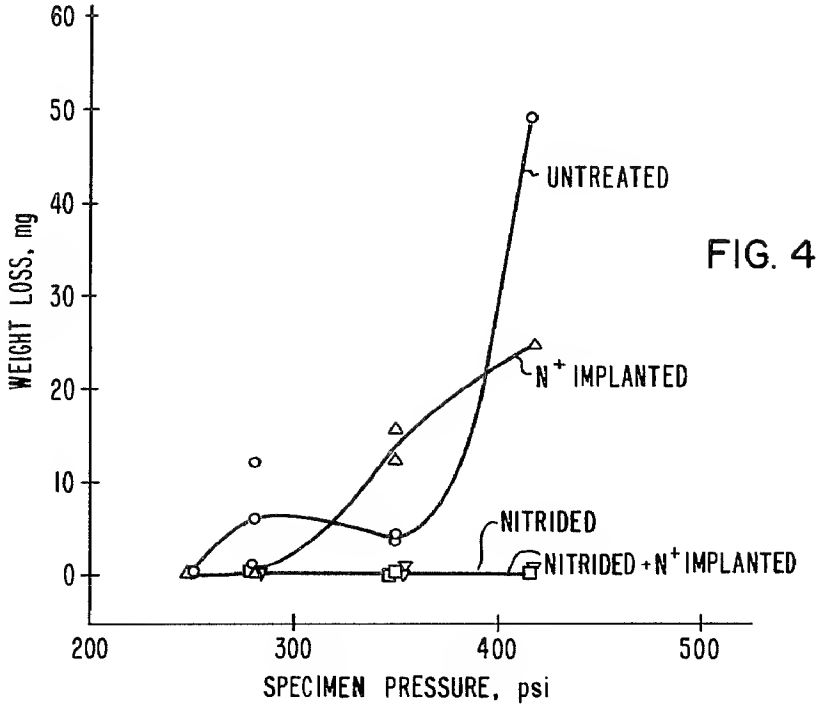
60
50
40
30
20
10
0
WEIGHT LOSS, mg
UNTREATED
N+ IMPLANTED
NITRIDED
NITRIDED + N+ IMPLANTED
200
300
400
500
SPECIMEN PRESSURE, psi

FIG. 4

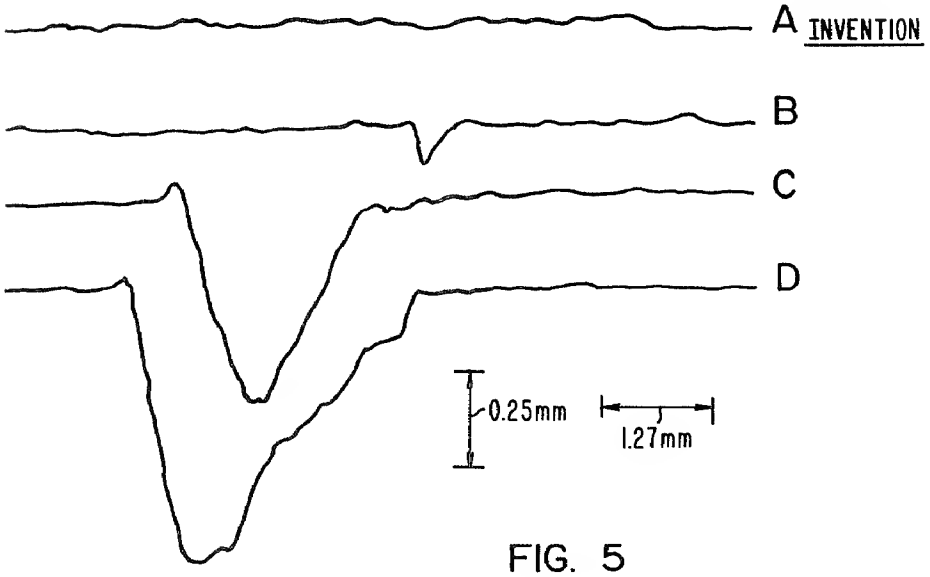
A INVENTION
B
C
D
0.25mm
1.27mm

FIG. 5

WEAR RESISTANT STEEL ARTICLES WITH CARBON, OXYGEN AND NITROGEN IMPLANTED IN THE SURFACE THEREOF

BACKGROUND OF THE INVENTION

The present invention relates to steels having high wear resistance and low friction surfaces and methods of producing these surfaces on steel.

In the past, the wear resistance of steel surfaces has been improved by subjecting the steel to a high temperature process in which a wear resistant coating is bonded to the surface or an element such as, carbon and/or nitrogen, is thermally diffused into the steel surface to locally increase the hardness of the steel itself in a relatively wide layer extending inwardly from the steel surface.

More recently, the use of ion implantation as a means for improving the wear resistance of steels and other alloys has begun to be explored. Ion implantation involves the implantation of a high energy, typically 10–400 keV, ionized species of atom or molecule into the surface being treated. The implanted ions are distributed in a relative thin band in a gaussian-like manner beneath the treated surface and produce a layer of irradiation hardened material in their wake. Thermal diffusion of the implanted species is insignificant since the process is carried out at a low temperature. Examples of ion implantation in steels are described in U.S. Pat. Nos. 3,900,636 and 3,832,219.

While improvements have been made in the wear and frictional properties of steel surfaces by the above processes, there still exists a need to provide further enhancement and optimization of these properties.

BRIEF SUMMARY OF THE INVENTION

In accordance with the present invention a steel member is provided having a low friction, high wear resistance surface layer formed by a process, also in accordance with this invention, which includes the steps of:

(1) diffusing nitrogen into the surface by thermal means;

(2) forming a carbon containing film on the nitrided steel surface;

(3) bombarding the carbon film and the steel surface with high energy ions thereby implanting the carbon into the steel surface.

The steel body produced by this process has a surface having overlapping layers beneath it including a layer enriched in nitrogen and a layer enriched in carbon. These layers overlap in a zone about 300 to 2500 angstroms wide.

Optionally in accordance with the present invention, a layer enriched in oxygen may also be provided by forming a thin oxide film on the surface of the steel and then subsequently implanting at least a portion of the oxygen in the film into the steel surface by bombarding it with high energy ions. The steel body produced by this embodiment of the invention has a zone beneath its surface enriched in oxygen, carbon and nitrogen to a depth of about 300 to 1000 angstroms below the steel surface.

These and other aspects of the present invention will become more apparent upon review of the following description of the invention in conjunction with the figures briefly described below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a wear and friction test couple used to test the present invention;

FIG. **2** demonstrates improvements in frictional force obtained by a surface treatment in accordance with the present invention;

FIGS. **3** and **4** demonstrate the improved wear resistance of a surface treatment in accordance with the present invention as measured by weight loss; and

FIGS. **5A–D** demonstrates the improved wear resistance of a surface treatment in accordance with the present invention as measured by surface profilometry after wear testing.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, a process for improving the wear resistance of conventionally nitrided steels has been discovered. The material treated in accordance with this invention has improved wear resistance compared to steels which have been only thermally nitrided or only nitrided by ion implantation.

The process according to this invention provides for the production of a relatively thick nitrided layer extending inwardly from one or more surfaces of a steel component. Typically, this layer is at least approximately 10 to 160 microns thick, and preferably about 20 to 40 microns thick. The maximum nitrogen concentration in this layer may be controlled between about 600 and 15,000 ppm. Any of the conventional thermal diffusion techniques, known to those skilled in the art, may be used to produce this nitrided layer. These techniques include both liquid and gas nitriding.

After the forming of the thermal diffusion nitride layer, a thin layer of carbon is implanted into the nitrided surface. Preferably, the carbon is implanted by bombarding a thin surface film containing carbon with a high energy ion specie so that a thin zone enriched in both carbon and nitrogen is formed beneath the steel surface. The layer containing carbon may be applied to the surface to be treated either during thermal nitriding (e.g. by carbonitriding techniques), in a separate step after thermal nitriding, during ion implantation itself, or by a combination of these techniques. A film of the elemental carbon may be applied to the surface during the ion implantation step by controlling the level of the vacuum in the target chamber containing the component to be implanted. It has been found that when the vacuum is maintained between about 10^{-4} to 10^{-3} Pa a layer of elemental carbon is placed on the surface due to the cracking of vacuum diffusion pump oil. A portion of this carbon is implanted into the surface of the steel. Preferably, nitrogen ions having an energy of 20 to 200 KeV and most preferably 50 to 150 KeV, are utilized to implant the carbon. The nitrogen ion fluence is preferably about 0.5×10^{17} to 2×10^{17} nitrogen ions/cm^2.

In addition to the above, an optional layer of oxygen may be implanted in the steel surface in much the same manner as the carbon was implanted, that is by recoil implantation. However, it is preferred that the oxide layer first be formed on the surface of the steel during thermal nitriding or during cooling from the thermal nitriding temperature. In this manner, a wear resistant steel surface is formed having a zone extending inwardly from it, of about 300 to 1000 angstroms wide which is enriched in carbon, oxygen and nitrogen.

The products produced by this process are characterized by significantly improved lubricated sliding wear resistance under pressures exceeding 300 to 400 psi. These products have an enriched zone beneath the surface containing carbon, nitrogen preferably up to about 15 atomic percent, optionally oxygen, and including iron and other elements contained in steel body.

A number of friction and wear test specimens were machined from 17-4 PH stainless steel (a registered trademark of ARMCO Steel Corp.) base stock. The specimen configurations, a cylinder **1** and disc **2** are shown in FIG. **1**. The cylinder **1** had an outside diameter of ½ inch and an inside diameter of ¼ inch. The disc had an outside diameter of slightly less than ¾ inch and a −3/32 diameter centrally located axial hole. Some of the specimens were gas nitrided as follows:

1. one hour at 524° C. in dissociated ammonia;
2. ten hours at 524° C. in 30% dissociated ammonia; and
3. cooled in dissociated ammonia to below 150° C.

Each step of the above treatment was performed at atmospheric pressure. This treatment yields a calculated nitrided depth of approximately 25 microns. A thin surface film containing oxygen and carbon was also produced during this treatment.

Some of the specimens in the untreated condition and some of the specimens in the nitrided condition were then ion implanted under the following conditions:

Fluence, N^+/cm^2	1×10^{17}
Ion	N^+
Beam Current, μA	500
Current Density, $\mu A/cm^2$	5.5
Beam Voltage, KeV	100
Beam Coverage, cm^2 (rastered)	91
Implantation Time, sec.	2919
Target Chamber Pressure, Pa (pascals)	$7\text{-}8 \times 10^{-4}$
Estimated Maximum Specimen Temperature, °C.	<50

As indicated by the following examples, machines having components, each having surfaces treated in accordance with this invention, and which are in sliding, lubricated contact with each other under a load, should offer distinct advantages from a wear and friction standpoint.

Sliding friction and wear tests were conducted on untreated, thermally nitrided, N^+ implanted and nitrided plus N^+ implanted disc and cylinder couples (i.e. having the same treatment history). The stationary disc **2**, shown in FIG. **1**, was fixed in a spring floated solid copper base cylinder (not shown). A chuck arrangement (not shown) allowed the rotating cylinder specimen **1** to be pressed down against the stationary disc specimen (race) **2** under a load (F_N) which could be varied at will. A transducer (not shown) attached to the copper base measured frictional force (F_F) which was continually recorded.

All tests were run under lubricated conditions using Chevron BRB-2-SRI, a standard petroleum lubricant containing a polyurea thickener and additives for improved oxidation stability and anti-wear characteristics. Each specimen couple was lubricated once, at the beginning of the test, which usually ran for 30 minutes. All tests were run by rotating the cylinder-shaped specimen at a speed of 1000 rpm. The wear specimens were ultrasonically cleaned in acetone, before and after the tests, and weight changes recorded.

In addition to measuring the wear damage by weight change, the specimens were examined by surface profilometer.

The wear and friction test results have indicated that these properties in the thermally nitrided and implanted material are superior to those found in the other conditions of the material. FIG. **2** presents the frictional force variations between similarly treated specimen couples as a function of time and load, F_N. Each column represents one surface condition and each row represents a different load. Two couples were utilized for some conditions (e.g., nitrided with F_N=229 N (newtons)). In general, the nitrided and N^+ implanted condition shows a reduction in the friction force compared to the untreated surface. Erratic variations in the frictional force are also largely absent for the nitrided and implanted condition, and improvements over the other surface conditions are most pronounced at the higher loads.

FIGS. **3** and **4** show the weight loss in milligrams as a function of pressure after 30 minutes of testing for the rotating cylinder and stationary disc, respectively. Overall, the specimen couples having a nitrided and ion implanted surface had superior wear resistance in comparison with any of the other surface treatments. This conclusion finds further support in the profilometer traces of the wear tracks produced in the stationary disc specimens tested at 416 psi. Typical traces are shown in FIG. **5** where (A) is the nitrided plus ion implanted surface, (B) is the thermally nitrided surface, (C) is the ion implanted surface, and (D) is the untreated surface.

The oxygen, nitrogen and carbon contents of the near surface regions of the 17-4 PH stainless steel specimens were semiquantitatively determined by Auger Electron Spectroscopy (AES) in conjunction with sputtering. Surfaces with each of the four treatment histories were analyzed. An argon ion beam was used to mill the surface at a rate of about 8 nanometers per minute. Spectra were taken at various depths. It was found that the nitrogen implantation did not produce a significant effect on the nitrogen concentration but did serve to recoil implant at least a portion of the oxygen and carbon atoms existing as a surface film about 300 to 500 angstroms wide on the thermally nitrided surface. The maximum nitrogen concentration beneath the surface did not significantly differ between the ion implanted, thermally nitrided and thermally nitrided plus ion implanted specimens, and was about 10 to 15 atomic percent. With respect to the carbon and oxygen contents, layers enriched significantly above the near surface carbon and oxygen concentrations produced by the other treatments were found in the nitrided and ion implanted material. These layers of enriched carbon and oxygen extended from the steel surface to depths of about 2500 angstroms and about 500 angstroms, respectively. The layer of nitrogen enrichment extended to depths significantly beyond those of the oxygen and carbon enriched layers. Analysis of the materials which were only thermally nitrided or nitrogen ion implanted showed no subsurface layers of significant thickness having a significant enrichment in oxygen or carbon. The thermally nitrided only material had an oxide and carbon containing film on its surface. The concentration of carbon in this carbon and oxygen containing film was approximately twice that found in the steel substrate. The ion implanted only material and the thermally nitrided and ion implanted material had a film of carbon on their implanted surfaces.

While the present invention has been described with respect to steel in general, and more particularly, with respect to stainless steel alloy 17-4 PH, it should be understood that this invention is also applicable to the other grades of stainless steel, including those which are of the precipitation hardening type. These embodiments are intended to be illustrative and are not intended as limitations on the scope of the coverage provided by the following claims.

We claim:

1. A steel member having a low friction, high wear resistance surface layer formed by the process comprising the steps of:

diffusing nitrogen into said surface by thermal means;

forming an oxygen containing film;

forming a carbon containing film on said surface;

then implanting nitrogen into said surface using accelerating beam voltages between about 10 and 400 KeV in a vacuum of about 10^{-4} to 10^{-3} Pa until a fluence of about 0.5×10^{17} to 2×10^{17} nitrogen ions/cm^2 is achieved; and wherein said implanting of nitrogen results in implanting carbon and oxygen into said surface from said carbon containing film and said oxygen containing film.

2. The steel member in accordance with claim 1 or 2 wherein an accelerating beam voltage of 50 to 150 KeV is used to implant said nitrogen ions.

3. The steel member according to claim 1 wherein said steel member is a stainless steel alloy.

4. The steel member according to claim 3 wherein said stainless steel alloy is a precipitation hardening alloy.

5. The steel member in accordance with claim 1 wherein said alloy is a type 17-4 PH stainless steel.

6. An article of manufacture comprising:

a steel body;

said steel body having a low friction, high wear resistance surface;

overlapping layers beneath said surface, including a layer enriched in nitrogen and a layer enriched in carbon, and wherein said layer enriched in nitrogen and said layer enriched in carbon overlap in a zone about 300 to 2500 angstroms wide;

and a layer enriched in oxygen overlapping said layer enriched in nitrogen and said layer enriched in carbon.

7. The article of manufacture in accordance with claim 6 wherein said zone contains oxygen, carbon, about 600 to 15,000 ppm nitrogen, and the balance consisting of iron and other elements present in said steel body.

8. The article according to claim 7 wherein said steel body is a stainless steel.

9. The article according to claim 8 wherein said stainless steel is a precipitation hardening type.

10. The article according to claim 9 wherein said stainless steel is a type 17-4 PH stainless steel.

* * * * *

EVIDENCE APPENDIX

EXHIBIT C

US005336518A

United States Patent [19]

Narayanan et al.

[11] Patent Number: 5,336,518

[45] Date of Patent: Aug. 9, 1994

[54] **TREATMENT OF METALLIC SURFACES USING RADIOFREQUENCY PLASMA DEPOSITION AND CHEMICAL ATTACHMENT OF BIOACTIVE AGENTS**

[75] Inventors: **Pallassana V. Narayanan,** Davie; **Stephen M. Rowland; Kimberly D. Stanley,** both of Miami, all of Fla.

[73] Assignee: **Cordis Corporation,** Miami Lakes, Fla.

[21] Appl. No.: **989,105**

[22] Filed: **Dec. 11, 1992**

[51] **Int. Cl.**[5] **A61F 2/00;** A61M 23/00

[52] **U.S. Cl.** **623/1;** 427/470; 427/2.25; 424/422; 424/423; 530/815; 530/816

[58] **Field of Search** 427/2, 490; 604/264, 604/265, 267; 530/402, 811, 812, 815, 816; 424/422, 423

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(List continued on next page.)

Primary Examiner—Asok Pal
Assistant Examiner—P. Achutamurthy
Attorney, Agent, or Firm—Lockwood, Alex, FitzGibbon & Cummings

[57] **ABSTRACT**

A treatment for metallic surfaces and devices having metallic surfaces is described. A film of heptafluorobutylmethacrylate (HFBMA) is applied to a surface by radiofrequency (RF) plasma deposition and subsequently treated with a biologically active agent. A water vapor RF plasma treatment of the HFBMA coating provides reactive groups thereon which can covalently bond to the biologically active agent. Alternatively, a spacer group can be bonded to the activated HFBMA and the biologically active agent can then be bonded to the spacer group. Devices coated according to the invention possess enhanced biocompatibility and the HFBMA coatings are durable even under severe crimping and expansion conditions.

16 Claims, 1 Drawing Sheet

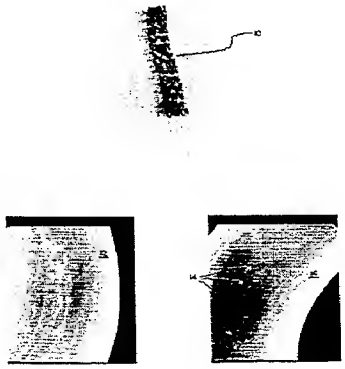

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FIG. 1

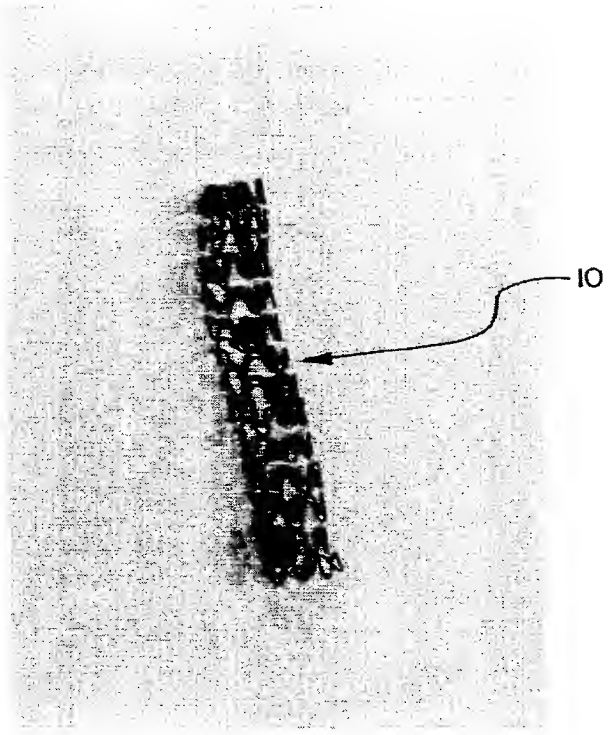


FIG. 2

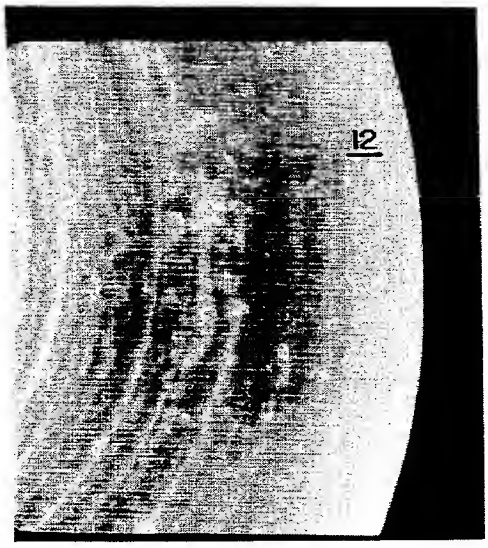
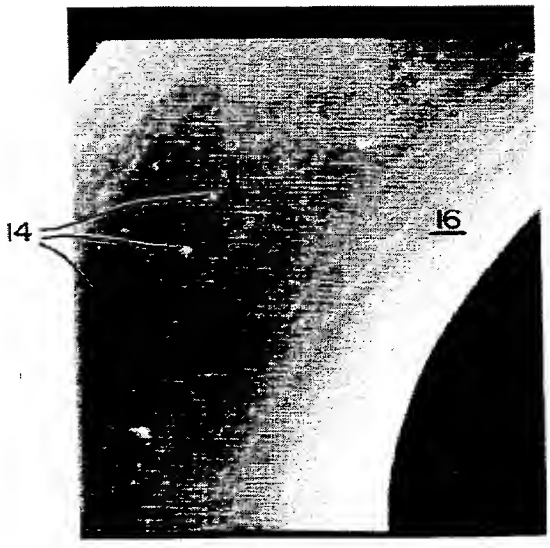


FIG. 3



TREATMENT OF METALLIC SURFACES USING RADIOFREQUENCY PLASMA DEPOSITION AND CHEMICAL ATTACHMENT OF BIOACTIVE AGENTS

BACKGROUND AND BRIEF DESCRIPTION OF THE INVENTION

The present invention generally relates to the treatment of metallic surfaces to enhance their biocompatibility and to medical devices and the like which include such biocompatible surfaces. More specifically, the invention relates to depositing a film of heptafluorobutylmethacrylate ("HFBMA") on a metallic surface using radiofrequency plasma deposition and subsequently functionalizing the deposited HFBMA by a water vapor radiofrequency plasma treatment. Biologically active agents are bound to the HFBMA coated surface so that medical devices which include such surfaces possess an improved biocompatibility.

Those skilled in the art will appreciate the importance of certain medical devices having surfaces of an enhanced biocompatibility. Medical devices made from polymeric materials as well as from metallic materials generally benefit from having enhanced biocompatibility especially where such devices are intended for subcutaneous implantation where they can experience in vivo environments depending on the nature of the particular device. The biocompatibility of such medical devices is generally enhanced by attempting to secure certain agents to the surface of those devices. For example, anti-thrombogenic agents are often secured to the surfaces of medical devices having blood contacting surfaces. It would be particularly undesirable to have the anti-thrombogenic agent leach away in wet environments such as those encountered by medical devices that engage blood or other body fluids.

Attempts have been made and approaches have been suggested for activating the surface of a medical device with a radiofrequency ("RF") plasma. The activated surface reacts with heparin or other biologically active agents to provide a biocompatible surface having specific characteristics such as Anti-thrombogenicity, endothelial growth promoters, and the like. The treatment of surfaces with a radiofrequency plasma has been described in various patents. Included are patents incorporating plasma discharge treatment with a gaseous environment including a variety of gases such as inert and organic gases. Patents in this regard include U.S. Pat. Nos. 4,613,517, 4,656,083 and 4,948,628, which mention a variety of plasma media including those generated from hydrogen, helium, ammonia, nitrogen, oxygen, neon, argon, krypton, xenon, ethylenic monomers and other hydrocarbons, halohydrocarbons, halocarbons and silanes. Certain of these plasma media are relatively expensive and can be hazardous to use within a manufacturing environment and/or to dispose of as waste. Certain plasma media are more suitable for treatment of specific substances.

Other surface treatments have been proposed specifically for metal surfaces intended to contact bodily fluids and the like during implantation. One such treatment involves the chemical oxidation of the metallic surface, such as a tantalum surface, until enough of a metal oxide layer is provided for bonding with a bioactive agent. Many other approaches in this area have concentrated on utilizing polymeric surfaces as the surface which encounters the body fluids and then treating those polymeric surfaces according to a variety of procedures. Polymeric surfaces and metallic surfaces each pose different problems which must be overcome to provide a polymeric or metallic surface that is suitable for implantation and/or extended-time residence within the body. U.S. Pat. Nos. 3,549,409 and 3,639,141 describe treatments of particular polymeric surfaces by swelling the polymeric surface, bonding an agent thereto and noncovalently coupling heparin to that agent. The latter of these patents mentions contacting the polymeric surface with an amino alkyl trialkoxysilane dissolved in an organic solvent to swell the polymeric material. Another approach involving a chemical treatment is exemplified by U.S. Pat. Nos. 4,526,714 and 4,634,762 which indicate that a surface can be rendered biocompatible by coating it with a conjugate of heparinous material and a protein, with the conjugate being formed by coupling carried out in the presence of 1-ethyl-3-dimethyl-aminopropyl carbodiimide (known as EDC) and the like as a coupling agent. The conjugate is attached to the substrate surface at the sites where the surface free functional groups suitable for bonding to the conjugate are present. In order to effect the coupling needed to form this conjugate, these free functional groups on the substrate surface are provided as free amino groups.

Another treatment procedure involves treatment of a surface with heparin benzalkonium chloride (HBAC). A quaternary amine structure is involved. The result is an ionic linkage, and subsequent ionic exchange occurs quite readily. For example, HBAC is easily leached from the treated surfaces to the extent that substantially all of the heparin is removed within about three days under leaching conditions. In addition, 4M guanidine, which is used to demonstrate the ionic nature of bonds by an ionic exchange mechanism, quickly removes the heparin in a one hour, non-physiological ionic release test. Furthermore, because benzalkonium chloride is in essence a surfactant, an HBAC conjugated surface is a cytotoxic material as well as a hemolytic material, causing a breakdown of red blood cells.

Other quaternary amine alternatives are believed to be non-hemolytic such as tetradodecylammonium chloride (TDAMC), for example. These types of materials are typically applied from a hydrocarbon solvent system, also providing ionic bonding and ionic exchange can and does occur quite readily. Because of its molecular structure, heparin and materials having similar functions do not escape quite as readily from TDAMC as from HBAC, but leaching is still very apparent. When attachment to a surface is by means of ionic bonding of TDAMC and the like, most of the heparin or bioactive agent is leached away after three hours of contact with blood plasma or after about 24 hours within a phosphate buffered saline solution under physiological conditions. The ionically attached material is substantially completely removed with guanidine within about one hour during non-physiological testing.

Many of the above-discussed attempts to improve the biocompatibility of various medical devices do not fare well under in vivo or biological conditions, and they fall short of fulfilling desirable attributes such as having the coating remain functional for a length of time adequate to provide maximum thrombus prevention. Another important consideration is whether the coating interferes with endothelialization. For metallic medical devices which undergo movements, such as bending of a

portion thereof during implantation and/or use, the mechanical properties of the treatment coating should be able to withstand flexure during bending, expansion and the like of the coated member. For example, metallic radially expandable generally tubularly shaped endoprostheses which are generally known as stents, must be able to withstand such flexure. An exemplary stent is described in U.S. Pat. No. 5,019,090, the subject matter thereof being incorporated by reference hereinto. Such stents are made of a very fine gauge metallic wire, typically tantalum or stainless steel wire. During implantation, these stents are mounted onto the balloon of an angioplasty catheter or the like until a partially occluded location within the blood vessel is reached, at which time the balloon and the stent are radially and circumferentially expanded for purposes of opening the occlusion and supporting the vessel at that location. This necessarily involves rather extensive bending of the tantalum wire. Many previously available coatings do not have the flexibility and/or adherence properties needed to avoid cracking and/or loss of the coating when subjected to this type of flexure.

It would be desirable to design and utilize a system which meets the objectives of imparting biocompatibility to a metallic substrate to thereby substantially prevent thrombus formation on the metallic surface. Such a system should not crack or otherwise deteriorate due to mechanical movement of the treated metallic member and the system should not allow substantial leaching of the biologically active material and should not substantially interfere with endothelialization after in vivo implantation.

It has been determined that a system providing covalent linkages between a bioactive agent and a functionalized HFBMA coated metal surface meets these objectives, providing an enhanced metallic surface with permanently improved biocompatibility. Such a system includes treating a metallic surface of the medical device with an RF plasma to deposit a film of HFBMA and subsequently functionalizing the deposited film by water vapor plasma treatment, thus providing available carboxy and hydroxy groups on the HFBMA coating to facilitate bonding with bioactive agents. The bioactive agents can be bound to the HFBMA surface using different reaction schemes and reagents including without limitation carbodiimide chemistry, organosilane chemistry, Woodwards K reagent and glutaraldehyde crosslinking. Various anti-thrombogenic agents, endothelial growth promoters, smooth muscle cell anti-proliferative agents, platelet growth factor antagonists, vasoconstrictors and vasodialators and cellular adhesion promoters can all be applied alone or in combination with spacers such as albumin, polyethylene oxide, various diacid chlorides, polyethyleneimine, N-(2-aminoethyl-3-aminopropyl) trimethoxysilane and the like.

The activated HFBMA-modified metallic surface may be treated with either a spacer or the bioactive agent using carbodiimide chemistry utilizing a water soluble carbodiimide. The molecule attached to the surface (either the HFBMA or the spacer) must have a primary or secondary amine and for a spacer there must be at least two primary or secondary amines. Endovascular stents can be made using these HFBMA coated metallic surfaces. There is evidence to show that a completely and quickly endothelialized object, such as a stent, does not promote smooth muscle cell proliferation and therefore could prevent restenosis.

It is accordingly a general object of the present invention to provide an improved biocompatible metallic surface, a method of preparing such a surface and a method of implanting a device having such a surface.

Another object of the present invention is to provide an improved stent or other medical device having a HFBMA coating which is capable of covalently bonding to bioactive agents and is able to withstand flexure and interaction with fluids.

Another object of this invention is to provide a method for depositing a film of HFBMA by radiofrequency plasma deposition and binding a bioactive agent thereto to provide an enhanced metallic surface with permanently improved biocompatibility.

Another object of the present invention is to provide an improved metallic surface which is particularly compatible and exhibits advantageous properties conducive to long-term placement within a body.

Another object of the present invention is to provide a treatment for metallic surfaces without detrimentally affecting the mechanical properties of the metal.

These and other objects, features and advantages of the present invention will be clearly understood by those skilled in the art through a consideration of the remainder of the disclosure, including the drawings and the detailed description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a reproduction of a photograph of a stent having an activated HFBMA coating with a covalently bonded heparin coating.

FIGS. **2, 3** are reproductions of SEM photographs of stents which have been treated according to the invention and subjected to canine blood in a closed flow system in which the blood is circulating over the sample for 5 minutes, to determine the blood-material interactions and specifically the effect of the device on the platelets in the blood.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides an improved biocompatible metallic surface for medical devices and the like by RF plasma deposition of HFBMA over the metallic surface followed by a suitable treatment with a biologically active agent. The resulting surface and/or device shows a permanently improved biocompatibility for in vivo use such as for endovascular stents and the like.

A metallic surface to be treated in accordance with the principles of the present invention is first coated with a film of HFBMA by RF plasma deposition and subsequently functionalized by water vapor RF plasma treatment to provide reactive carboxy and hydroxy groups to facilitate the subsequent bonding of the biologically active agent thereto. The modified HFBMA surface may be treated with either a spacer or bioactive agent having a primary or secondary amine and for a spacer molecule there should be at least two primary or secondary amines to form a covalent bond between the carboxy group of the activated HFBMA and the amine on the spacer or bioactive molecule. The reaction between the HFBMA and the bioactive agent typically proceeds by a condensation reaction or peptide bond formation using a carbodiimide coupling agent to form a covalent bond between the carboxy group of the activated HFBMA and the amine of the bioactive agent.

Although carbodiimide chemistry is one mechanism by which the HFBMA and the bioactive agent are covalently bonded, different reaction schemes and reagents will also produce the desired result. Such schemes and reagents include without limitation organosilane chemistry, Woodwards K reagent as well as glutaraldehyde cross-linking. Numerous bioactive agents can be used in practicing the invention including anti-thrombogenic agents such as heparins, hirudin, hyaluronic acid and PPACK (D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone); endothelial growth promotors such as vascular endothelial growth factor, gelatin, fibronectin, collagen, laminin, matrigel, and victronectin; smooth muscle cell anti-proliferative agents such as anti-β-FGF, meulinolin, enoxaparin and 5-fluorouracil; platelet growth factor antagonist; vasoconstrictors and vasodilators; and cellular adhesion promoters.

While the bioactive agents may be applied directly to the HFMBA coating, it may be desirable to first attach a spacer group prior to treating the surface with the bioactive agent. Suitable spacer groups include albumin, polyethyleneimine and N-(2-aminoethyl--3-aminopropyl) trimethoxysilane. Where the bioactive molecule is bound through an organosilane spacer molecule, the reaction is a condensation reaction between the hydroxy groups on the HFBMA coating and the silane functionality on the organosilane. The bioactive molecule is subsequently bound to the amine of the silane by carbodiimide chemistry.

While virtually any metallic surface can experience an enhanced biocompatibility by a treatment of the surface in accordance with the principles disclosed herein, for convenience and simplicity the disclosure frequently discusses the application of the invention in the context of treating endovascular stents such as the stent **10** of **FIG. 1**. Those skilled in the art will understand that the broader teachings of the invention apply to any metallic surface where an enhanced biocompatability is desired.

In coating a metallic surface of a stent or the like with HFBMA, an RF plasma deposition technique is used and the HFBMA coating is subsequently activated using water plasma treatment. In preparing stents by plasma polymerization, stents are mounted on a metal mount and loaded into a one inch diameter, twelve inch long glass reactor tube. The reactor is RF coupled capacitively by external electrodes and the system is pumped down to remove air. Water and oxygen are introduced into the reactor in a three-to-one ratio and the pressure is adjusted to 100 mtorr. Fifty watts of RF is applied to pretreat the stents with a water/oxygen plasma. After pretreatment, the system is pumped down to remove water and oxygen. Nitrogen and HFBMA are next introduced into the reactor while pressure is maintained at 250 mtorr using a pressure controller system. RF power at 20 watts is then applied for 3.5 minutes to obtain a HFBMA coating. The system is again pumped down to remove the residual HFBMA monomer and nitrogen. Water vapor is introduced into the reactor while pressure is controlled at 400 mtorr and RF power at 20 watts is applied to create a water vapor plasma for 45 seconds to modify the polymer coating obtained in the HFBMA treatment step.

Once the HFBMA coating has been deposited and subsequently activated, the activated surface can be treated with either a bioactive agent or a spacer molecule, as discussed herein. Typically, an aqueous solution of the spacer or bioactive agent is applied to the activated HFBMA coating with an amount of a carbodiimide compound to facilitate a condensation or peptide bond formation using the carbodiimide as a coupling agent. As a coupling agent, the carbodiimide will covalently bond to both the carboxy group on the HFBMA and the amine on the spacer molecule or the bioactive agent. An aqueous solution of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) is a suitable coupling agent. Preferably, the EDC concentration on a weight per volume basis is approximately equal and up to twice the concentration of the spacer or the bioactive agent and is typically between about 4.0 mg/ml and about 8.0 mg/ml. Most typically, where heparin is employed as the bioactive agent, a 1:1 ratio of heparin:EDC is desired. A carbodiimide is not required with an organosilane spacer group since a condensation reaction will occur between the hydroxy groups of the activated HFBMA surface and the hydroxy groups of the silane functionality.

Where a spacer molecule is added directly to the HFBMA coating, the stent is typically placed in a solution of the spacer and exposed to the solution for several minutes. Where a spacer such as polyethylenimine (PEI) is used, a PEI concentration of about 1% by weight is generally adequate with the stent being exposed to the solution for about 5 minutes. Other spacers may require different exposure times depending upon the spacer and the concentration thereof. A stent exposed to a solution of albumin at a concentration of 3.33 mg/ml typically requires exposure to the solution for approximately 15 minutes. Following exposure to the spacer solution, the stent is typically rinsed and/or air dried for a suitable period of time and, in the case of silane spacer, the stent may be oven cured at an elevated temperature of between about 100° C. and about 120° C.

The bioactive agent may be added to the spacer in an aqueous or other suitable solution. The addition of heparin to the spacer is typically accomplished by exposing the stent to an aqueous heparin solution for a period of time between about 20 minutes and about 90 minutes. Where carbodiimide chemistry is employed in bonding the heparin with the spacer molecule, EDC is typically added to the heparin solution to facilitate bonding. A heparin concentration of 6.67 mg/ml with an equal concentration of EDC has been suitable. Of course, other bioactive agents can be used such as hyaluronic acid as well as hirudin, for example. Where heparin is the bioactive agent, the presence of the heparin coating on a stent may be confirmed by known techniques such as by extraction in phosphate buffered saline (PBS) followed by rinsing and staining with toluidine blue. A change in the light refraction will indicate that the samples have picked up the purple color of the dye which commonly occurs in the presence of heparin. Staining the treated stents with berberine sulfate, a fluorescent stain, and an examination of the stained stents under a fluorescent microscope will show a yellow glow in the presence of heparin. Fluorescent thrombin-anti-thrombin (TAT) immunoassay is another technique available to determine the presence of biologically active heparin.

Stents that have been treated according to the invention generally have shown improved durability over stents that have been treated by other techniques to improve their biocompatibility. Coatings of the invention are suitable for deposition on electropolished as well as non-polished metallic surfaces, displaying an improved durability for both surfaces. Non-polished

stents, for example, may present at least the potential for irritation of blood vessel lumen due to roughness of non-polished metallic surfaces. The complications can be avoided since the coatings of the present invention will durably adhere to electropolished surfaces. Also, as set forth herein, flow loop analysis performed on stents made in accordance with the invention has demonstrated low platelet activation as well as low platelet adherence, suggesting a reduction in the release of platelet factors which trigger smooth muscle cell migration and phenotypic change. The lack of muscle cell migration would limit the smooth muscle cell proliferation which is one component of the stenosis pathway, suggesting that the coating of the invention may play a part in the prevention of restenosis. Flow loop analysis has shown the coatings of the invention to be generally superior to prior art coatings with no adverse effects on the coagulation system. FIGS. **2** and **3** are illustrative of flow loop data for stents coated according to the invention. The FIGS. **2** and **3** represent SEM photographs, taken at a magnification of 1500× of stents coated with HFBMA-albumin-heparin and subjected to flow loop analysis. The SEM field shown in FIG. **2** reveals no adherent platelets on the stent surface **12**, and, the field shown in FIG. **3** reveals only four platelets **14** on the stent surface **16**.

The following examples illustrate the inventive biocompatible coatings for metal surfaces and the advantageous properties thereof.

EXAMPLE 1

Stent samples were coated with HFMBA using plasma deposition and the HFBMA coating was activated by water plasma treatment. The coated and activated samples were then treated with an aqueous solution of polyethylenimine (PEI) and EDC with a PEI concentration of 1% by weight and 5 mg/ml EDC at an overall pH of 8. The stent samples were exposed to the PEI:EDC solution for five minutes and were then removed from the solution and rinsed. Heparin was applied from an aqueous solution having a heparin concentration of 6.67 mg/ml with an equal concentration of EDC at an overall pH of 3. The stents were exposed to the heparin for one hour and were then rinsed and air dried. Samples were then extracted in phosphate buffered saline (PBS) for three hours at physiological temperature. The samples were removed and rinsed and then stained with toluidine blue. The light refraction for the samples indicated that the stents had picked up the purple color of the dye, indicating the presence of heparin.

EXAMPLE 2

Stents samples were coated with HFBMA and activated as in Example 1 followed by a treatment with a 2% solution of [3-(2 aminoethyl) aminopropyl] trimethoxysilane for five minutes after which the samples were removed from the solution and air dried for about one minute to remove excess solvent (95% ethanol). The samples were oven cured at 110° C. for ten minutes and then cooled. The stents were exposed to the heparin solution of Example 1 for one hour, and were then rinsed and air dried. The presence of heparin on the stents was confirmed using a PBS extraction as in Example 1.

EXAMPLE 3

Stent samples were treated with HFBMA and activated as in Example 1. Each of the samples were then treated with an aqueous albumin:EDC solution containing 3.33 mg/ml albumin and 6.67 mg/ml EDC. The samples were allowed to sit in the albumin:EDC solution for 15 minutes at a pH of about 5. After fifteen minutes, the samples were removed from the solution and rinsed completely and then placed in a heparin-:EDC solution identical to the solution of Example 1. The samples were treated in the heparin solution for thirty minutes and then removed, rinsed and allowed to air dry.

EXAMPLE 4

Stent samples were treated as in Example 3 except that the albumin concentration was 2.5 mg/ml and the EDC concentration was 5mg/ml at an overall pH of about 5. The presence of heparin on the stents was confirmed by PBS extraction as in Example 1. Additionally, a TAT immunoassay was performed on the samples by first incubating the samples in human blood plasma and then rinsing and incubating the samples in a solution of fluorescently labeled anti-thrombin. The stents were examined under fluorescent microscope to confirm the presence of biologically active heparin, as indicated by a yellow glow of the sample surfaces. The biologically active heparin was evenly distributed on the samples. Finally, berberine staining was also performed by staining the stents with fluorescent stain berberine sulfate followed by an examination of the samples under a fluorescent microscope, showing a relatively even yellow glow indicative of the presence of heparin.

EXAMPLE 5

Stents samples which had been electropolished were then treated as in Example 2.

EXAMPLE 6

Stents samples which were previously electropolished were then treated as in Example 4 herein.

EXAMPLE 7

Durability (expansion) testing was conducted on stents prepared according to Examples 1, 2, 4, 5 and 6 to determine the durability of the coating on the stent after the stent had been crimped onto a balloon and then expanded. The analysis was done using a scanning electron microscope (SEM). Results of the examination indicated that although crimping caused some abrasions of the stent coatings, there were no breaks in any of the examined coatings and all of the samples showed a uniform coating covering the entire surface of the stent.

EXAMPLE 8

Flow loop analysis was performed on stent samples prepared as in Examples 4 and 6. This analysis was used to characterize the interaction of platelets with the stent samples. Decalcified blood was passed through a polymethylmethacrylate flow cell containing a stent sample for five minutes. Testing done on the blood both before and after the analysis included activated partial thrombo plastin time (APTT), hemolysis and total blood counts (CBC). Platelet aggregation testing was performed prior to beginning the experiment to determine if the platelets in the blood were acceptable after

blood transport to the site of the experiment. Following flow loop analysis, samples were fixed with glutaraldehyde and dehydrated with an ethanol series. SEM analysis was performed to determine the per unit area of platelets adhering to the samples. The samples coated with the HFBMA:albumin:heparin coating on either an electropolished or a non-polished wire exhibited very few platelets adhering to the surface. In some fields, no platelets were observed. The average number of platelets per field was approximately three and platelets that did adhere were observed as spherical and showing little to no signs of activation (e.g. no spreading, cytoplasmic streaming or pseudopod formation was observed). Control samples showed moderate to strong platelet adhesion with the platelets showing signs of activation along with the presence of pseudopods.

EXAMPLE 9

A comparison was made of coated tantalum stents by comparison of flow loop data collected for four stents having various coatings. The data for these stents is presented in Table I. The coated stents included an HFBMA coated stent without a bioactive agent bonded thereto, and another HFBMA coated stent which was further treated to include an albumin spacer group and a heparin coating bonded thereto. A third stent was coated with an aminosilane coating which also included a coating of heparin. A fourth stent was coated with a coating known under the trademark SPI-LON TM, of the Spire Corporation of Bedford, Mass., a polytetrafluoroethylene which is ion-beam sputtered onto the surface of the stent. The control was an uncoated, unpolished tantalum stent.

The aminosilane-heparin coating showed many adherent platelets under SEM examination. The SPI-LON TM coated stent gave very low platelet counts and the two HFBMA-treated stents experienced no adherent platelets in the fields examined by SEM. Additionally, the ability to bond heparin and other bioactive agents to the surface of the HFBMA coating is an advantage over the SPI-LON TM coated stents, enhancing the performance of the device in a targeted area of the body.

TABLE I

Comparative Flow Loop Data	
Stent Coating	Flow Loop (avg. no. platelets/.006 mm^2)
HFBMA	0
HFBMA - Albumin-Heparin	0
Aminosilane-Heparin	11
SPI-LON TM	2
(Control)	Massive platelet aggregates on internal diameter of stent

The above examples illustrate various features of the invention as well as the manner in which devices can be made hereunder. It should now be appreciated that devices, such as the endovascular stents discussed herein, are rendered more biocompatible when coated with the inventive HFBMA/bioactive agent coatings disclosed herein as opposed to prior art coatings. Generally, the coatings of the invention possess improved durability and/or improved biocompatability over other commonly used prior art coatings. For example, the hydrophilic polymer coating known under the trade name HYDROMER TM may satisfactorily endure certain durability testing but typically shows poor hemocompatibility. A xylene-based polymer coating such as PARALENE C TM demonstrates poor hemocompatibility, showing no significant differences from uncoated control samples. Moreover, the PARALENE C TM coating is easily disrupted during durability testing, experiencing plastic deformation and even slight disruption of the coating. Similarly, certain tetrafluoroethylene (TFE) coatings and coatings made from hyaluronic acid will typically experience massive disruption under crimping and expansion testing. The coatings of the present invention, however, are biocompatible while also being very durable.

It will be understood that the embodiments of the present invention which have been described are illustrative of some of the applications of the principles of the present invention. Modifications may be made by those skilled in the art without departing from the true spirit and scope of the invention.

What is claimed is:

1. A method for rendering biocompatible a metal surface of a medical device, comprising the steps of:
   coating said metal surface with a layer of heptafluorobutylmethacrylate monomer to form a polymer coating on said surface;
   treating said polymer coating with water vapor plasma to provide reactive groups thereon; and
   applying a biologically active agent to said polymer coating;
   the thus formed device being a biocompatible metallic member which, when implanted within a blood vessel, prevents substantial thrombus from occurring on its surface while not significantly interfering with endothelialization of said surface.

2. The method of claim 1 wherein the step of treating said polymer coating further includes applying a spacer molecule thereto, said spacer molecule forming a covalent linkage with said polymer coating; and said applying of said biologically active agent is performed after said spacer molecule is applied to said polymer coating, said biologically active agent and said spacer molecule also forming a covalent linkage therebetween.

3. The method of claim 1 wherein the step of coating said metal surface with a layer of heptafluorobutylmethacrylate is accomplished using a radio frequency plasma deposition thereof; and the step of treating said polymer coating by water vapor is also accomplished by a radio frequency plasma treatment of said polymer coating.

4. The method of claim 1 wherein the step of applying a biologically active agent includes exposing the polymer coating to an aqueous heparin solution having a heparin concentration of between about 4.0 mg/ml and about 8.0 mg/ml for a period of between about 30 and about 90 minutes.

5. The method of claim 4 wherein the step of exposing the polymer coating to an aqueous heparin solution is accomplished in the presence of a carbodiimide compound in solution with said heparin and at a concentration approximately equal to the concentration of said heparin.

6. The method of claim 5 wherein said carbodiimide is N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride.

7. The method of claim 2 wherein said spacer molecule is albumin, an alkyleneimine or an alkoxysilane and the step of applying a spacer molecule is accomplished by exposing said polymer coating to a solution of said

spacer molecule for a period of between about two minutes and about thirty minutes.

8. The method of claim **7** wherein the step of applying a spacer molecular is accomplished by exposing the polymer coating to an aqueous solution of albumin or polyethyleneimine, said solution also including at least about 5.0 mg/ml of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride.

9. The method of claim **7** wherein the step of applying a spacer molecule is accomplished by exposing the polymer coating to a solution of trimethoxysilane in 95% ethanol for a period of at least about 3 minutes.

10. A medical device having a biocompatible antithrombogenic metallic surface, comprising:

a metallic surface having a biologically active treatment adhered thereto;

said biologically active treatment including a coating of heptafluorobutylmethacrylate polymer having reactive groups thereon, and a biologically active agent covalently bonded to said reactive groups;

whereby the biocompatible metallic surface, when implanted within a blood vessel, substantially prevents thrombus formation thereon while avoiding any significant interference of the development of endothelialization of the biocompatable metallic surface.

11. The medical device of claim **10** wherein said metallic surface is an endovascular stent.

12. The medical device of claim **10** wherein said biologically active agent is selected from the group consisting essentially of heparins, hirudin, hyaluronic acid, D-phenylalanyl-L-proyl-L-arginine chloromethyl ketone, vascular endothelial growth factor, gelatin, fibronectin, collagen, laminin, matrigel, victronectin, anti-β-FGF, meulinolin, enoxaparin, 5-fluorouracil, platelet growth factor antagonist, vasoconstrictors and vasodilators, and cellular adhesion promotors.

13. A medical device having a biocompatible antithrombogenic metallic surface, comprising:

a metallic surface with a biologically compatible treatment adhered thereto;

said biologically active treatment including a heptafluorobutylmethacrylate polymer coating adhered to said metallic surface, a spacer molecule covalently bonded to said polymer coating and a biologically active agent covalently bonded to said spacer molecule;

whereby, the biocompatible metallic member, when implanted within a blood vessel, prevents substantial thrombus from occurring on its surface while not significantly interfering with endothelialization of said surface.

14. The medical device of claim **13** wherein said metallic surface is an endovascular stent.

15. The medical device of claim **13** wherein said spacer molecule is selected from a group consisting essentially of albumin, polyethyleneimine, and N-(2-aminoethyl-3-aminopropyl) trimethoxysilane.

16. The medical device of claim **13** wherein said biologically active agent is selected from the group consisting essentially of heparins, hirudin, hyaluronic acid, D-phenylalanyl--L-proyl-L-arginine chloromethyl ketone, vascular endothelial growth factor, gelatin, fibronectin, collagen, laminin, matrigel, victronectin, anti-β-FGF, meulinolin, enoxaparin, 5-fluorouracil, platelet growth factor antagonist, vasoconstrictors and vasodilators, and cellular adhesion promotors.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,336,518

DATED : August 9, 1994

INVENTOR(S) : Pallassana V. Narayanan, Stephen M. Rowland and Kimberly D. Stanley

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Col. 1, lines 27-28, "in vivo" should be in italics; line 43, "Anti-thrombogenicity" should read --anti-thrombogenicity--.
Col. 2, line 62, "in vivo" should be in italics.
Col. 3, line 32, "in vivo" should be in italics.
Col. 4, line 6, "having a" should read --having an--; lines 48-49, "in vivo" should be in italics.
Col. 5, lines 22-23, "N-(2-aminoethyl---3-aminopropyl)" should read --N-(2-aminoethyl-3-aminopropyl)--; line 57, "obtain a" should read --obtain an--.
Col. 8, line 26, "under fluorescent" should read --under a fluorescent--.
Col. 11, line 4, "molecular" should read --molecule--; line 32, "D-phenylalanyl-L-proyl-L-arginine" should read --D-phenylalanyl-L-prolyl-L-arginine--.
Col. 12, line 28, "D-phenylalanyl--L-proyl-L-arginine" should read --D-phenylalanyl-L-prolyl-L-arginine--.

Signed and Sealed this

Tenth Day of October, 1995

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

EVIDENCE APPENDIX

EXHIBIT D

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TYSON, MELANIE RUANO	
ART UNIT	**PAPER NUMBER**
3773	

MAIL DATE	DELIVERY MODE
04/04/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,449	MALIK ET AL.	
	Examiner	Art Unit	
	MELANIE TYSON	3773	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/28/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the applicant's amendment received 28 January 2011. The application is not in condition for allowance for the reasons set forth below. Claims 2, 3, 7, 11, 12, and 14-30 remain cancelled.

Response to Arguments

The applicant's arguments with respect to the combination of Taylor and Ecer have been fully considered but they are not persuasive. The applicant argues that one would not look to Ecer to modify Taylor's stent (i.e., non-analogous art). However, Ecer suggests that carbon is a known material for increasing the hardness of steel (for example, see column 1, lines 14-18). Stainless steels having improved hardness yield stents having increased tensile strength, stiffness, and resistance to radial compression, thus improving the performance of the stent within, for example, a pulsating lumen. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide Taylor's stainless steel stent body with a carbon deposit as taught by Ecer in order to provide the stent with these advantages. The applicant also argues that method of implanting carbon near the surface of the stent as taught by Ecer would not result in a change in properties in the vast majority of the stent, and since no significant improvement in tensile strength, stiffness, and resistance to radial compression of the stent would be observed, one would not look to Ecer to modify Taylor (as described in an affidavit submitted). However, since at least a local increase in hardness is achieved, it is the examiner's position one having ordinary skill in the art would look to Ecer to modify Taylor to achieve such improvements throughout

the stent. In response to the applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned from the applicant's disclosure, such a reconstruction is proper. The applicant has not provided any arguments directed to the Narayanan reference and thus the combination fr Taylor and Ecer with Narayanan is still deemed proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-6, 8-10, 13, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (U.S. Patent No. 6,083,257 - cited on 892 dated

6/6/08), Ecer et al. (U.S. Patent No. 4,486,247 - cited on 892 dated 6/6/08), and Narayanan et al. (U.S. Patent No. 5,336,518-cited on 892 dated 6/23/09).

Taylor discloses a stent (see entire document) comprising a radially expandable metallic stent body formed of a stainless steel alloy (for example, see column 5, lines 51-56 and lines 62- 63) having a polymer film in intimate contact with the tissue contacting surface of the stent (for example see column 3, lines 63-67). Taylor fails to disclose the stent body comprises a carbon deposit.

Ecer discloses a stainless steel base material being modified by having carbon implanted within the surface of the stainless steel base material at a depth from about 300 to about 2500 angstroms, or of about 300 to about 1000 angstroms below the steel surface, which falls within the claimed range (for example, see column 1, lines 50-54 and 60-64). Ecer suggests that carbon is a known material for increasing the hardness of steel (for example, see column 1, lines 14-18). It is well known in the art that stainless steels having improved hardness yield stents having increased tensile strength, stiffness, and resistance to radial compression, thus improving the performance of the stent within, for example, a pulsating lumen. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide Taylor's stainless steel stent body with a carbon deposit as taught by Ecer in order to provide the stent with the advantages described above. Taylor as modified by Ecer fails to disclose the polymer film layer comprises an acrylate and is chemically bonded to the carbon deposit.

Narayanan discloses a metallic stent comprising a polymer film (see entire document). Narayanan teaches polymer films containing acrylate, such as HFBMA, enhance metallic surfaces with permanent improved biocompatibility. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide Taylor's device, as modified by Ecer, with a polymer film containing acrylate as taught by Narayanan. Doing so would improve the biocompatibility of the device. Narayanan further teaches the film is applied to the metallic surface via plasma polymerization deposition. The applicant discloses in the specification that depositing films to stents via plasma polymerization deposition is well known in the art, wherein "one having ordinary skill in the art will recognize that some fragmentation of the acrylate typically occurs during the plasma polymerization deposition of the film layer, resulting in an acrylate-like polymer layer of fragmented acrylate, which will be covalently bonded to carbon deposits." Therefore, by the applicant's own admission, applying Narayanan's acrylate containing polymer film via Narayanan's technique of plasma polymerization deposition to Taylor's device as modified by Ecer would yield a device in which the polymer film layer is covalently bonded to the carbon deposit as recited in the claims.

For examination purposes, claim 5 is being treated as a product by process limitation, in that "the plasma-polymerized polymer film is formed by exposing the stent to an acrylic acid plasma" refers to the process of forming the plasma-polymerized polymer film and not to the final product created. As set forth in MPEP 2113, "Even though product-by-process claims are limited by and defined by the process,

determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product in the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695,698,227 USPQ 964,966 (Fed. Cir. 1985). Examiner has evaluated the product claim without giving much weight to the method of its manufacture. Therefore, in this case, a plasma-polymerized polymer film formed by exposing the stent to an acrylic plasma is directed to the method of making the polymer film and not to the final product made. It appears that the product disclosed by Taylor as modified by Ecer and Narayanan would be the same, especially since both applicant's product and the prior art product have the same final structure of a metallic stent having a plasma-polymerized polymer film layer chemically bonded thereto.

With further respect to claim 6, Narayanan discloses the activated acrylate may comprise functional groups such as carboxylate or amine (for example, see column 3, line 43 and 62-63).

With further respect to claim 10, Narayanan also teaches bioactive agents formed on the plasma polymerized polymer film (for example, see column 3, lines 44-56). It would have been obvious to one having ordinary skill in the art at the time the invention was made to form a therapeutic substance on the modified film layer above as taught by Narayanan in order to enhance treatment and promote healing at the treatment site.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELANIE TYSON whose telephone number is (571)272-9062 and e-mail address is Melanie.tyson@uspto.gov. The examiner can normally be reached on Monday through Thursday 8-7 (IFP).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jackie Ho can be reached on (571) 272-4696. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melanie Tyson/
Primary Examiner, Art Unit 3773
March 28, 2011

EVIDENCE APPENDIX

EXHIBIT E

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,449	11/30/2001	Shamim M. Malik	050623.00134	3441

45159 7590 08/31/2010

SQUIRE, SANDERS & DEMPSEY LLP
275 BATTERY STREET, SUITE 2600
SAN FRANCISCO, CA 94111-3356

EXAMINER	
TYSON, MELANIE RUANO	
ART UNIT	PAPER NUMBER
3773	
MAIL DATE	DELIVERY MODE
08/31/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,449	MALIK ET AL.	
	Examiner	Art Unit	
	MELANIE TYSON	3773	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the appeal brief filed on 24 June 2010, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below. Claims 2, 3, 7, 11, 12, and 14-30 remain cancelled.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/(Jackie) Tan-Uyen T. Ho/

Supervisory Patent Examiner, Art Unit 3773.

Response to Arguments

Applicant's arguments with respect to the combination of Taylor and Ecer with Kraus and Narayanan have been considered but are moot in view of the new ground(s) of rejection (see new rejection below).

The applicant's arguments with respect to the combination of Taylor and Ecer have been fully considered but they are not persuasive. The applicant argues that one would not look to Ecer to modify Taylor's stent, since Ecer is directed to the issue of wear and abrasion resistance and is not in the field of medical devices. However, medical devices are formed of different materials in which wear and abrasion resistance are concerns of medical devices implanted within the body. Therefore, one having ordinary skill in the art would look to Ecer to modify Taylor's stent. The applicant also argues that implanting carbon near the surface of the stent as taught by Ecer would not result in a change in properties in the vast majority of the stent and since no significant improvement in tensile strength, stiffness, and resistance to radial compression of the stent would be observed, one would not look to Ecer to modify Taylor. However, since some improvement may be observed, it is the examiner's position one having ordinary skill in the art may look to Ecer to modify Taylor to achieve such improvement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-6, 8-10, 13, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (U.S. Patent No. 6,083,257 - cited on 892 dated 6/6/08), Ecer et al. (U.S. Patent No. 4,486,247 - cited on 892 dated 6/6/08), and Narayanan et al. (U.S. Patent No. 5,336,518-cited on 892 dated 6/23/09).

Taylor discloses a stent (see entire document) comprising a radially expandable metallic stent body formed of a stainless steel alloy (for example, see column 5, lines 51-56 and lines 62- 63) having a polymer film in intimate contact with the tissue contacting surface of the stent (for example see column 3, lines 63-67). Taylor fails to disclose the stent body comprises a carbon deposit.

Ecer discloses a stainless steel base material being modified by having carbon implanted within the surface of the stainless steel base material at a depth from about 300 to about 2500 angstroms, or of about 300 to about 1000 angstroms below the steel surface, which falls within the claimed range (for example, see column 1, lines 50-54 and 60-64). Ecer suggests that carbon is a known material for increasing the hardness of steel (for example, see column 1, lines 14-18). It is well known in the art that stainless steels having improved hardness yield stents having increased tensile strength, stiffness, and resistance to radial compression, thus improving the performance of the stent within, for example, a pulsating lumen. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide Taylor's stainless steel stent body with a carbon deposit as taught by Ecer in order to

provide the stent with the advantages described above. Taylor as modified by Ecer fails to disclose the polymer film layer comprises an acrylate and is chemically bonded to the carbon deposit.

Narayanan discloses a metallic stent comprising a polymer film (see entire document). Narayanan teaches polymer films containing acrylate, such as HFBMA, enhance metallic surfaces with permanent improved biocompatibility. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide Taylor's device, as modified by Ecer, with a polymer film containing acrylate as taught by Narayanan. Doing so would improve the biocompatibility of the device. Narayanan further teaches the film is applied to the metallic surface via plasma polymerization deposition. The applicant discloses in the specification that depositing films to stents via plasma polymerization deposition is well known in the art, wherein "one having ordinary skill in the art will recognize that some fragmentation of the acrylate typically occurs during the plasma polymerization deposition of the film layer, resulting in an acrylate-like polymer layer of fragmented acrylate, which will be covalently bonded to carbon deposits." Therefore, by the applicant's own admission, applying Narayanan's acrylate containing polymer film via the known technique of plasma polymerization deposition to Taylor's device as modified by Ecer would yield a device in which the polymer film layer is covalently bonded to the carbon deposit as recited in the claims.

For examination purposes, claim 5 is being treated as a product by process limitation, in that "the plasma-polymerized polymer film is formed by exposing the stent

to an acrylic acid plasma" refers to the process of forming the plasma-polymerized polymer film and not to the final product created. As set forth in MPEP 2113, "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product in the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695,698,227 USPQ 964,966 (Fed. Cir. 1985). Examiner has evaluated the product claim without giving much weight to the method of its manufacture. Therefore, in this case, a plasma-polymerized polymer film formed by exposing the stent to an acrylic plasma is directed to the method of making the polymer film and not to the final product made. It appears that the product disclosed by Taylor as modified by Ecer and Narayanan would be the same, especially since both applicant's product and the prior art product have the same final structure of a metallic stent having a plasma-polymerized polymer film layer chemically bonded thereto.

With further respect to claim 6, Narayanan discloses the activated acrylate may comprise functional groups such as carboxylate or amine (for example, see column 3, line 43 and 62-63).

With further respect to claim 10, Narayanan also teaches bioactive agents formed on the plasma polymerized polymer film (for example, see column 3, lines 44-56). It would have been obvious to one having ordinary skill in the art at the time the invention was made to form a therapeutic substance on the modified film layer above as

taught by Narayanan in order to enhance treatment and promote healing at the treatment site.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELANIE TYSON whose telephone number is (571) 272-9062 and e-mail address is Melanie.tyson@uspto.gov. The examiner can normally be reached on Monday through Thursday 8-7 (max flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jackie Ho can be reached on (571) 272-4696. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Melanie Tyson /M. T./
Examiner, Art Unit 3773
August 26, 2010

EVIDENCE APPENDIX

EXHIBIT F

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,449	11/30/2001	Shamim M. Malik	050623.00134	3441

45159 7590 12/24/2009

SQUIRE, SANDERS & DEMPSEY LLP
1 MARITIME PLAZA
SUITE 300
SAN FRANCISCO, CA 94111

EXAMINER	
TYSON, MELANIE RUANO	
ART UNIT	PAPER NUMBER
3773	

MAIL DATE	DELIVERY MODE
12/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,449	MALIK ET AL.	
	Examiner	Art Unit	
	MELANIE TYSON	3773	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the applicant's amendment received 23 October 2009. The amendment does not place the application in condition for allowance for the reasons set forth below. Claims 2, 3, 7, 11, 12, and 14-30 are cancelled.

Affidavit

Declaration under 37 CFR §1.132

When all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness. Dr. Pamela Kramer-Brown declares that implanting carbon near the surface of the stent, as taught by Ecer, would not result in a change in properties in the vast majority of the stent and since no significant improvement in tensile strength, stiffness, and resistance to radial compression of the stent would be observed, one would not look to Ecer to modify Taylor. However, since some improvement may be observed, it is the examiner's position one having ordinary skill in the art may look to Ecer to modify Taylor to achieve such improvement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-6, 8-10, 13, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (U.S. Patent No. 6,083,257 - cited on 892 dated 6/6/08), Ecer et al. (U.S. Patent No. 4,486,247 - cited on 892 dated 6/6/08), Narayanan et al. (U.S. Patent No. 5,336,518), and Kraus et al. (U.S. Patent No. 6,712,846 B1).

Taylor discloses a stent (see entire document) comprising a radially expandable metallic stent body formed of a stainless steel alloy (for example, see column 5, lines 51-56 and lines 62- 63) having a polymer film in intimate contact with the tissue contacting surface of the stent (for example see column 3, lines 63-67). Taylor fails to disclose the stent body comprises a carbon deposit.

Ecer discloses a stainless steel base material being modified by having carbon implanted within the surface of the stainless steel base material at a depth from about 300 to about 2500 angstroms, or of about 300 to about 1000 angstroms below the steel surface, which falls within the claimed range (for example, see column 1, lines 50-54 and 60-64). Ecer suggests that carbon is a known material for increasing the hardness of steel (for example, see column 1, lines 14-18). It is well known in the art that stainless

steels having improved hardness yield stents having increased tensile strength, stiffness, and resistance to radial compression, thus improving the performance of the stent within, for example, a pulsating lumen. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide Taylor's stainless steel stent body with a carbon deposit as taught by Ecer in order to provide the stent with the advantages described above.

Taylor discloses the polymer film is applied to the stent surface by dipping methods, thus Taylor as modified by Ecer fails to disclose the polymer film layer is "chemically" bonded to the carbon deposit. Kraus discloses a polymer coated metallic stent (see entire document). Kraus teaches the polymer may be applied to the metallic stent by chemical vapor deposition (for example, see column 5, lines 39-41 and claim 27), thus chemically bonding the polymer film to the metallic stent. Thus, it would have been recognized by one of ordinary skill in the art that applying the known technique taught by Kraus to the metallic stent of Taylor as modified by Ecer would have yielded predicable results and resulted in an improved system, namely, a metallic stent with a carbon deposit having a polymer film chemically bonded thereto (i.e., to the stent including materials within the stent body such as the carbon deposit), thus reducing the risk of the film inadvertently coming off of the stent during handling and/or deployment.

Taylor also fails to disclose the polymer film is plasma polymerized. Narayanan discloses a metallic stent comprising a polymer film (see entire document). Narayanan teaches plasma polymerized films, such as HFBMA (which is an acrylate), to enhance metallic surfaces with permanent improved biocompatibility. Narayanan also teaches

bioactive agents (or "therapeutic substance"; see claim 10 of the current application) formed on the plasma polymerized polymer film (for example, see column 3, lines 44-56), wherein the plasma-polymerized polymer film also provides a stronger bond with the bioactive agents, since covalent linkages are formed between the film and the agents (for example, see column 3, lines 34-44). It would have been obvious to one having ordinary skill in the art at the time the invention was made to form a therapeutic substance on Taylor's film layer as taught by Narayanan in order to enhance treatment and promote healing at the treatment site. Furthermore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to utilize a plasma polymerized polymer film in Taylor's invention as taught by Narayanan in order to provide the advantages described above. With further respect to claim 4, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide a film layer comprising an acrylate material as taught by Narayanan, since it has been held to be within the general skill of a worker in the art to select a known material on the basis of its suitability for the intended use as a matter of design choice. With further respect to claim 6, Narayanan discloses the activated acrylate may comprise functional groups such as carboxy or amine (for example, see column 3, line 43 and 62-63).

For examination purposes, claim 5 is being treated as a product by process limitation, in that "the plasma-polymerized polymer film is formed by exposing the stent to an acrylic acid plasma" refers to the process of forming the plasma-polymerized polymer film and not to the final product created. As set forth in MPEP 2113, "Even

though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product in the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695,698,227 USPQ 964,966 (Fed. Cir. 1985). Examiner has evaluated the product claim without giving much weight to the method of its manufacture. Therefore, in this case, a plasma-polymerized polymer film formed by exposing the stent to an acrylic plasma is directed to the method of making the polymer film and not to the final product made. It appears that the product disclosed by Taylor as modified by Ecer, Kraus, and Narayanan would be the same, especially since both applicant's product and the prior art product have the same final structure of a metallic stent having a plasma-polymerized polymer film layer.

Response to Arguments

Applicant's arguments filed 23 October 2009 with respect to claims 1, 4-6, 8-10, 13, and 31 have been fully considered but they are not persuasive.

The applicant argues that one would not look to Ecer to modify Taylor's stent, since Ecer is directed to the issue of wear and abrasion resistance and is not in the field of medical devices. However, medical devices are formed of different materials in which wear and abrasion resistance are concerns of medical devices implanted within the body. Therefore, one having ordinary skill in the art would look to Ecer to modify Taylor's stent. The applicant also argues that implanting carbon near the surface of the

stent, as taught by Ecer, would not result in a change in properties in the vast majority of the stent and since no significant improvement in tensile strength, stiffness, and resistance to radial compression of the stent would be observed, one would not look to Ecer to modify Taylor. However, since some improvement may be observed, it is the examiner's position one having ordinary skill in the art may look to Ecer to modify Taylor to achieve such improvement.

The applicant then argues that although Kraus discloses the polymer coating may be applied using chemical vapor deposition, Kraus fails to disclose such a process causes chemical or covalent bonding to the stent. However, Kraus discloses such a process forms covalent bonding (for example, see claim 27 and column 3, lines 31-43).

The applicant further argues if one were to use the chemical vapor deposition method of Kraus to apply the polymer coating, the coating would not be a plasma polymerized polymer film layer, and on the other hand, if one were to use a plasma polymerization method of Narayanan to apply the coating, the coating would not be chemically bonded. However, one method is not being used in place of the other. The plasma polymerized polymer film layer of Narayanan is chemically bonded to the substrate as taught by Kraus.

The applicant finally argues there is nothing in any of the four references utilized that discloses the implantation of carbon in the surface of a stent increases adhesion of a coating to the surface. However, the fact that the applicant uses the implantation of carbon in the surface of a stent for a different purpose does not alter the conclusion

that its use in Taylor would have been obvious to one having ordinary skill in the art as taught by Ecer.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELANIE TYSON whose telephone number is (571)272-9062. The examiner can normally be reached on Monday through Friday 7-7 (max flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jackie Ho can be reached on (571) 272-4696. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Melanie Tyson /M. T./
Examiner, Art Unit 3773
December 17, 2009

/(Jackie) Tan-Uyen T. Ho/
Supervisory Patent Examiner, Art Unit 3773

EVIDENCE APPENDIX

EXHIBIT G

US006712846B1

(12) **United States Patent**
Kraus et al.

(10) **Patent No.: US 6,712,846 B1**
(45) **Date of Patent: *Mar. 30, 2004**

(54) **POLYMER-COATED STENTS, PROCESSES FOR PRODUCING THE SAME AND THEIR USE FOR RESTENOSIS PREVENTION**

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(73) Assignees: **Schering Aktiengesellschaft**, Berlin (DE); **Angiomed GmbH & Co. Medizintechnik KG**, Karlsruhe (DE)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/403,923**

(22) PCT Filed: **Apr. 29, 1998**

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§ 371 (c)(1),
(2), (4) Date: **Jun. 5, 2000**

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PCT Pub. Date: **Nov. 5, 1998**

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Apr. 30, 1997 (DE) 197 18 339

(51) **Int. Cl.**[7] **A61F 2/06**
(52) **U.S. Cl.** **623/1.46**; 623/1.1; 623/1.42
(58) **Field of Search** 623/1.1, 1.41–1.43, 623/1.46–1.48, 1.11; 600/3; 604/103.02; 514/772.2, 449

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* cited by examiner

Primary Examiner—Julian W. Woo
(74) *Attorney, Agent, or Firm*—Millen, White, Zelano & Branigan, P.C.

(57) **ABSTRACT**

The invention relates to polymer-coated stents, processes for their production and their use for restenosis prevention.

33 Claims, No Drawings

POLYMER-COATED STENTS, PROCESSES FOR PRODUCING THE SAME AND THEIR USE FOR RESTENOSIS PREVENTION

The invention relates to stents with polymer coating, processes for their production and their use for preventing restenosis.

THE PRIOR ART

Stents are prior art (Pschyrembel, Klinisches Wörterbuch [Clinical Dictionary], 257^{rh} edition, W. de Gruyter Publisher). Stents are endoprostheses that make it possible to keep duct-like structures open in the bodies of humans or animals (e.g., vessel, esophageal, tracheal, bile duct stent). They are used as palliative measures for constrictions by closure (e.g., atherosclerosis) or by external pressure (e.g., from tumors). Radioactive stents are used for restenosis prevention, for example, after surgical intervention in the vessels or interventional radiological procedures (e.g., balloon angioplasty).

The surface of the previously described stents is either metallic and consists, e.g., of stainless steel, nitinol or gold, or is covered with a layer of a polymer, e.g., with polyurethane, polylactic acid, polyglycolic acid or copolymers.

Stents are also known that are coated with a polymer layer that contains a therapeutic agent and gradually releases it. Such a stent is described, e.g., in patent application WO 91/12779.

In European patent application EP 0 819 446 A2, a stent coated with a chelating agent is described. The stent is dipped in a solution with a radioisotope before implantation, so that a radioactive implant is achieved. But in contrast to other therapeutic agents, the radioisotope is not to reach the blood stream. But in the stents proposed in this application, the selected chelating agents all have poor properties as complexing agents, so that it is not guaranteed that the radioisotope remains bonded to the stent.

Now the problem exists that the stent, for the body, is a foreign object and intolerance reactions occur. Further, it must be guaranteed for a radioactive implant that the radioactive isotope is permanently bonded to the surface and will not come off in vivo.

The object of this invention is thus to make available stents that are tolerated better than conventional stents and to whose surface therapeutic agents are bonded. If radioisotopes are used as therapeutic agents, then the radioactive isotopes must be permanently bonded to the stent surface so that the radioactive ions do not come off in vivo.

This object is achieved by the stents described below as they are characterized in the claims.

DESCRIPTION OF THE INVENTION

The object outlined above is achieved according to the invention in that the surface of the stent is coated with a polymer to which hydrophilic substances are coupled that additionally can represent or contain a therapeutic agent.

The device according to the invention thus consists of a base stent element to which a polymer is applied that carries hydrophilic substances having a particular affinity for therapeutic agents.

Commercially available implants can be used as base elements, e.g., a nitinol, stainless steel or gold stent. The Memotherm® stent, Wiktor stent, Strecker Stent or Palmaz-Schatz stent are common. Nitinol stents are preferably used.

Modified polyurethanes to whose surface hydrophilic substances are coupled, e.g., polyethylene glycols, polysaccharides, cyclodextrins or polyaminopolycarboxylic acids can be considered as polymers.

The therapeutic agents form either complexes with the hydrophilic substances (e.g., radioactive metal ions form very stable metal complexes with DTPA) or inclusion compounds (e.g., cyclodextrin forms a very stable inclusion compound with Iloprost).

To the extent that the hydrophilic substances have complexing properties, they can fix metal ions or radioactive isotopes. Polyaminopolycarboxylic acids, crown ethers, bis-oligo- or polyphosphonates, oligo- or polypeptides, sugar such as chitosan or cyclodextrin derivatives are examples of complexing chelating agents.

Polyaminopolycarboxylic acids in the context of this document are, e.g., DTPA, DOTA, DO3A, TTHA and their derivatives. Let us also mention, as examples, the compounds BOPTA, butylphenyl-DTPA, DTPA-BMEA, DTPA-BMA, dicyclohexyl-DTPA, dicyclohexyl-DOTA, DPDP, DTPA- or DOTA-substituted polymers, GlyMeDOTA such as GlyMeDOTA-substituted polymers and porphyrin derivatives.

The radioactive isotopes of the elements Ag, Au, Ba, Bi, C, Co, Cr, Cu, Fe, Ga, Gd, Hg, Ho, In, Ir, Lu, Mn, P, Pb, Pd, Pm, Re, Rh, Ru, Sb, Sc, Sm, Tb, Tc or Y can be used as radioactive isotopes.

The stents according to the invention can be produced, for example, as follows:

1. With Stents Coated with Radiotherapeutic Agents

1.1 An uncoated stent can first be coated with a polymer (e.g., a polyurethane, obtainable from the reaction of an amphiphilic polyether, diphenylmethane-4,4'-diisocyanate and butanediol). This polymer is modified so that it carries complexing agents (e.g., DTPA groups) on the surface. The polymer is dissolved in a solvent (e.g., chloroform) and the stent is dipped in the polymer solution. After removal of the stent from the polymer solution, it is dried in a drying chamber at room temperature. The hydrophilic stent is ready for use.

1.2 The stent coated according to 1.1 is treated with a solution of radioactive metal (e.g., $^{111}InCl_3$, ^{90}Y). After washing the stent, this stent, coated radiotherapeutically, is ready for use.

1.3 In a variant of this process, the stent is coated in two stages. For this purpose, first the stent is treated with a polymer containing amino groups. The amino groups are present optionally in protected form during the polymerization. Then the amino groups are reacted with DTPA-monoanhydride, as it is described in the literature. The stent now has a polymer coating containing complexing agents (here: DTPA). The stent coated this way is then treated with a solution of radioactive metal (e.g., $^{111}InCl_3$, ^{90}Y). After washing the stent, it is ready for use.

1.3. In another variant of the process, the stent coated with the bonding agent (polymer containing complexing agents) is implanted in an organism. A solution of a radioactive isotope is then administered intravascularly. In this process, the stent is coated radioactively in vivo. In this variant, the complexing agent portion of the bonding agent can be coated with physiologically tolerated metals (e.g., sodium, calcium, zinc, potassium, lithium, magnesium) to increase the tolerance of the implant. Thus, e.g., calcium ions can be complexed by the DTPA groups.

2. Stents Coated with Nonradioactive Therapeutic Agents

2.1 An uncoated stent can first be coated with a polymer (e.g., a polyurethane, obtainable from the reaction of an amphiphilic polyether, diphenylmethane-4,4'-diisocyanate and butanediol). This polymer is modified so that is has cyclodextrin on the surface. The polymer is dissolved in a solvent (e.g., chloroform) and the stent is dipped in the polymer solution. After removing the stent from the polymer solution, it is dried in a drying chamber at room temperature. The hydrophilic stent is ready for use.

2.2 The stent coated according to 2.1 is treated with a solution of the therapeutic agent (e.g., Iloprost). The therapeutic agent forms an inclusion compound with the cyclodextrin and stays bonded to the stent. After washing, the therapeutically coated stent is ready for use. The above-described processes are generally performed at temperatures of 0–80° C. Suitable solvents can be used for coating the stent depending on the respective polymer. When a nonaqueous solvent is used, it should be removed before implantation.

The radioactive stents can also be coated with two or more different isotopes. In particular it is possible to apply short- and long-lived isotopes together on one stent (e.g., ^{55}Co with ^{55}Fe or ^{99}Mo with ^{57}Co).

The work steps necessary to perform the processes described in principle above are known to one skilled in the art. Particular embodiments are described in detail in the examples.

Another process for the production of polymer-coated, radioactive stents is based on the process disclosed in German laid-open specification DE 196 04 173 A1, a process for creating antithrombogenic surfaces on medical objects. In this process, a functionalized polymer is applied to the base metal element of the stent by chemical vapor deposition at increased temperatures and reduced pressures. If a polymer containing an amino group is applied, then the stent can be treated after the polymer coating with a solution that contains a complexing agent in reactive form, e.g., DTPA-anhydride. A chemical reaction causes a true bonding, e.g., covalent bonding, between the polymer and the complexing agent. Alternatively, the polymer-coated stent can also be treated with spacer molecules such as, e.g., diisocyanates or dicarboxylic acid chlorides to which, in another reaction step, the complexing agent is bonded. A spacer molecule in the context of this application is a molecule that is suited for a chemical joining between the polymer surface and the complexing agent and provides the effect of a spacer.

The complexing agents used are, e.g., DTPA, DOTA, DO3A, and TTHA, which all have especially good complexing properties. They form especially stable complexes with metal ions so that, after dipping a stent coated with polymer and complexing agents in a solution with radioactive metal ions, these ions remain bonded to the surface of the stent. The stability of the metal complex is so good that the metal ions do not come off the implant even in vivo. Preferred isotopes are ^{186}Re, ^{188}Re, ^{111}In, ^{90}Y, ^{55}Co, ^{57}Co, ^{55}Fe and ^{99}Mo. It is also possible in this embodiment to apply several radioisotopes simultaneously to the stent. The radioisotopes can emit β or γ radiation.

Further, the radioactive stents according to the invention can also be produced by applying the polymer layer, with the help of plasma polymerization of olefins, to the base stent element. This process is described, e.g., in German laid-open specification DE 196 47 280 A1. Suitable olefins are, e.g., allylamine, allylalcohol, propargyl alcohol, butenols, butylamines, acrylic acid, acrylic acid derivatives, acrylates and hydroxymethyl acrylate. Complexing agents can be bonded either directly or by a spacer molecule to the functional groups of the polymer layer produced this way. The stents produced this way also are preferably treated before implantation with solutions containing radioactive metal ions of the isotopes ^{186}Re, ^{188}Re, ^{111}In, ^{90}Y, ^{55}Co, ^{57}Co, ^{55}Fe and ^{99}Mo.

It is also possible to apply to the stent, in addition to the radioactive substances, medicines such as Iloprost. Prostaglandin derivatives such as Iloprost can be inserted, as described above, in cyclodextrin derivatives located on the modified polymer surface.

The stents according to the invention achieve the above-described object. The stents according to the invention are well tolerated physiologically.

Stents containing complexing agents can be tagged radioactively with exact dosing by the disclosed processes without problems. As was able to be shown in the animal model, restenosis after balloon denudation was significantly inhibited by implantation of the radioactive stent according to the invention.

The particular advantage of the stent according to the invention is that the medical practitioner can select a stent according to his needs in advance and then activate the selected stent by the described process. The activation is performed by adding one or more radioactive isotopes and/or by applying one or more medicines that are inserted in the carrier (chelating agent or cyclodextrin). This makes it possible to adjust to the individual needs of the respective patient. The few materials and solutions needed for it can be delivered suitably prepared so that the medical practitioner in question need only dip the still uncoated stent in the predetermined sequence in the individual solutions. The invention thus relates also to materials, solutions, and preparations (kits) prepared for the process according to the invention.

Another advantage of the radioactive stent according to the invention is that, because of the especially good complexing properties of the selected chelating agents, the radioisotopes are so permanently bonded to the polymer surface that they do not come off the stent surface in vivo and/or are not exchanged for other ions. The tolerance of the radioactive stent according to the invention is considerably increased in comparison to the known radioactive stents.

EXAMPLES

The following examples are to explain the object of the invention in a nonlimiting way.

Example 1

^{188}Re-DTPA-loaded Stent

Polyurethane, obtainable by reacting an amphiphilic polyether, diphenylmethane-4,4'-diisocyanate and butanediol as a chain lengthener, is used as the polymer. To increase the yield of groups able to couple, additional functions, such as e.g., amino groups, can be contained in the individual components and they can optionally be present in protected form during the polymerization. The stents are coated by dipping them in a 5% chloroform solution of the polymer. Afterward, they are left to dry in a clean-room drying chamber at room temperature. The average layer thickness is 20 μm. The coating with the DTPA ligands is performed by reacting free amino groups with DTPA monoanhydride, as it is described in the literature and is known to one skilled in the art. The complexing is

performed, also as is known to one skilled in the art, with a solution of a rhemium salt. Then the stent is ready for use.

Example 2

^{111}In-DTPA Stent Kit

The coating of the stent with the polymer and the subsequent reaction with DTPA monoanhydride are performed as described in example 1. The stent is now delivered in this form to the radiologist. Shortly before administration, the radiologist dips the stent in a solution with ^{111}In ions, to activate it this way. Then the stent is implanted.

Example 3

^{111}In-DTPA Stent Kit

The coating of the stent with the polymer is performed as described in example 1. The stent is now delivered in this form to the radiologist. Shortly before administration, the radiologist dips the stent in a solution of DTPA monoanhydride, to apply the ligands to the stent. After taking the stent out of the solution and drying it, the subsequent reaction with ^{111}In ions is performed. For this purpose, the stent is dipped in a second solution containing ^{111}In ions, to activate it this way. After drying it again, the stent is implanted.

Example 4

^{111}In-DTPA Stent Kit

The coating of the stent with the polymer and the subsequent reaction with DTPA monoanhydride are performed as described in example 1. The stent is now delivered in this form to the radiologist. After administration of the stent, the radiologist injects a solution with radioactive ^{111}In ions through the application catheter. This solution flows by the implanted stent and the radioisotopes are selectively removed from the solution by the ligands bonded to the stent and are fixed permanently on the stent.

Example 5

The coating of a metal stent by chemical vapor deposition (CVD) polymerization of 4-amino-[2,2]-paracyclophane is performed in a suitably designed unit. The unit is connected to an argon pressure cylinder, since argon functions as the carrier gas. The argon feed is with a 380 mm-long quartz glass tube with an outer diameter of 30 mm. The quartz glass tube is connected on its other end to a stainless steel pressure container. The quartz glass tube is supported floating freely in a three-zone tube furnace with a heated length of 320 mm and an inner diameter of 32 mm. All three heating zones can be heated to 800° C.

The stent to be coated is fixed by the removable viewing glass to the sample container. Then the reactor is closed again and the unit begins operation by activation of the main switch. Simultaneously, both cooling cycles are activated and the pressure container wall is heated to 100° C. Then a porcelain boat with a weighed-in amount of monomer is placed in the sublimation zone and the latter is closed again. The reactor is then evacuated to a base pressure of 0.03 mbar. Now a carrier gas stream of 20 sccm is started and then a working pressure of 0.2 mbar is established. Now a constant carrier gas flow and working pressure are awaited. Now the desired pyrolysis temperature of 680° C. is set and one waits until this temperature is reached in the pyrolysis zone. Then the sample container is made. to rotate with a rotation speed of 20 revolutions/min and the sublimation zone is heated to 290° C. The coating process is verified with the help of the layer thickness monitor. When the desired layer thickness of 280 nm is reached, the coating process can be ended. For this purpose the furnace controller, the torque motor of the sample container and the carrier gas stream are shut off, the flow control valve is opened and evacuated again to base pressure. Then the pump is turned off, the unit is ventilated with the ventilator valve, and the sample is removed.

To couple DTPA by a spacer molecule, the coated stent is incubated in 500 ml of a 10% by weight ethereal hexamethylenediisocyanate solution for 12 hours at room temperature. Then the sample is washed with ether and dried in a vacuum. Then the stent coated this way is incubated with a solution of DTPA anhydride in DMSO for 2 hours at 40° C. After cleaning it again, the surface is charged in the usual way with ^{188}Re ions.

What is claimed is:

1. A polymer-coated stent, comprising a base stent on which a polymer is applied that has a hydrophilic chelating or inclusion agent covalently bonded to the surface thereof, and has one or more radioisotopes and/or one or more therapeutic agents either complexed with the hydrophilic chelating or inclusion agent or forms an inclusion compound with the hydrophilic chelating or inclusion agent on the surface of the stent.

2. A polymer-coated stent according to claim **1**, wherein the hydrophilic chelating or inclusion agent is DTPA, DOTA, DO3A, or TTHA or a derivative thereof.

3. A polymer-coated stent according to claim **1**, wherein the hydrophilic chelating or inclusion agent is BOPTA, butylphenyl-DTPA, DTPA-BMEA, DTPA-BMA, dicyclohexyl-DTPA, dicyclohexyl-DOTA, DPDP, a perhydrin derivative, a DTPA- or DOTA-substituted polymer, GlyMeDOTA or a GlyMeDOTA-substituted polymer.

4. A polymer-coated stent according to claim **1**, wherein the one or more radioisotopes are selected from the group consisting of radioisotopes of the elements Ag, Au, Ba, Bi, Co, Cr, Cu, Fe, Ga, Gd, Hg, Ho, In, Ir, Lu, Mn, Pb, Pd, Pm, Re, Rh, Ru, Sb, Sc, Sm, Tb, Tc, Mo and Y.

5. A polymer-coated stent according to claim **4**, wherein the one or more radioisotopes are selected from the group consisting of ^{186}Re, ^{188}Re, ^{111}In, ^{90}Y, ^{55}Co, ^{57}Co, ^{55}Fe and ^{99}Mo.

6. A polymer coated stent of claim **4**, wherein the radioisotopes are permanently bonded to the polymer surface.

7. A polymer coated stent of claim **4**, wherein the radioisotopes are ^{55}Co and ^{55}Fe or ^{99}Mo and ^{57}Co.

8. A polymer-coated stent according to claim **1**, wherein the base stent is a nitinol stent.

9. A polymer-coated stent according to claim **1**, wherein the hydrophilic chelating or inclusion agent is a cyclodextrin.

10. A polymer-coated stent according to claim **9**, wherein the one or more therapeutic agents is a prostaglandin derivative.

11. A polymer-coated stent according to claim **1**, wherein one or more radioisotopes are complexed with the hydrophilic chelating or inclusion agent or form an inclusion compound with the hydrophilic chelating or inclusion agent on the surface of the stent.

12. A polymer-coated stent according to claim **11**, wherein the therapeutic agent is iloprost.

13. A polymer-coated stent according to claim **1**, wherein the one or more therapeutic agents is a prostaglandin derivative.

14. A method for treating or preventing stenoses, comprising implanting a stent according to claim **1** into a blood vessel.

15. A polymer-coated stent according to claim **1**, wherein the hydrophilic chelating or inclusion agent is a complexing agent.

16. In a method of implanting a stent into a patient, wherein the stent is a polymer-coated stent according to claim 1.

17. A kit comprising a polymer-coated stent according to claim 1 and one or more solutions, each solution comprising one or more radioactive isotopes and/or one or more therapeutic agents.

18. A method of preparing a stent by using a kit according to claim 17, comprising dipping the polymer-coated stent into the one or more solutions.

19. A method of preparing a polymer-coated stent according to claim 1, comprising dipping an uncoated stent into one or more solutions, each solution comprising one or more polymers, one or more radioactive isotopes, one or more therapeutic agents, and one or more hydrophilic chelating or inclusion agents.

20. A method according to claim 19, wherein the hydrophilic chelating or inclusion agent is cyclodextrin.

21. A polymer-coated stent according to claim 1, wherein the hydrophilic chelating or inclusion agent is a therapeutic agent, or wherein the hydrophilic chelating or inclusion agent has an affinity for a therapeutic agent.

22. A polymer-coated stent according to claim 21, wherein the hydrophilic chelating or inclusion agent that has as affinity for a therapeutic agent forms a complex with a therapeutic agent, or forms an inclusion compound with a therapeutic agent, in a manner that the complex or inclusion compound are carried on the surface of the polymer.

23. A polymer coated stent according to claim 1, wherein the polymer is polyurethane, polylactic acid, polyglycolic acid or copolymers thereof.

24. A polymer coated stent according to claim 1, wherein the polymer is a polyethylene glycol, a polysaccharide, a cyclodextrin or a polyaminopolycarboxylic acid.

25. A polymer-coated stent according to claim 1, consisting essentially of a base stent on which a polymer is applied that has a hydrophilic chelating or inclusion agent covalently bonded to the surface thereof, and has one or more radioisotopes and/or one or more therapeutic agents either complexed with the hydrophilic chelating or inclusion agent or forms an inclusion compound with the hydrophilic chelating or inclusion agent on the surface of the stent.

26. A polymer-coated stent according to claim 1, consisting of a base stent on which a polymer is applied that has a hydrophilic chelating or inclusion agent covalently bonded to the surface thereof, and has one or more radioisotopes and/or one or more therapeutic agents either complexed with the hydrophilic chelating or inclusion agent or forms an inclusion compound with the hydrophilic chelating or inclusion agent on the surface of the stent.

27. A process for preparing a polymer-coated stent, comprising coating a metallic base stent by chemical vapor deposition with a polymer that has functional groups, and covalently bonding a hydrophilic chelating or inclusion agent by chemical reaction to the functional groups.

28. A process for preparing a polymer-coated stent, comprising coating a metallic base by chemical vapor deposition with a polymer that has functional groups, then treating the coated metallic base stent with a solution that contains spacer molecules whereby the spacer molecules covalently bond to the functional groups, and then further treating the coated metallic base stent with a solution that contains a hydrophilic chelating or inclusion agent that covalently bonds to the spacer molecules and/or the functional groups that do not contain a spacer molecule.

29. A process for preparing a polymer-coated stent, comprising coating a base stent with a polymer having functional groups by plasma polymerization, and covalently bonding a hydrophilic chelating or inclusion agent by chemical reaction to the functional groups.

30. A process for preparing a polymer-coated stent, comprising coating abase stent with a polymer having functional groups by plasma polymerization, then treating the coated base stent with a solution that contains spacer molecules whereby the spacer molecules covalently bond to the functional groups, and then further treating the base stent with a solution that contains a hydrophilic chelating or inclusion agent that covalently bonds to the spacer molecules and/or the functional groups that do not contain a spacer molecule.

31. A process for preparing a polymer-coated stent, comprising coating a metallic base stent with a polymer having functional groups by chemical vapor deposition, and covalently bonding a cyclodextrin derivative by chemical reaction to the functional groups.

32. A process for preparing a polymer-coated stent, comprising coating a metallic base stent with a polymer having functional groups by chemical vapor deposition, then treating the coated metallic base stent with a solution containing spacer molecules whereby the spacer molecules covalently bond to the functional groups, and then further treating the base stent with a solution containing a cyclodextrin derivative that covalently bonds to the spacer molecules and/or the functional groups that do not contain a spacer molecule.

33. A polymer-coated stent, comprising a base stent on which a polymer is applied that has a hydrophilic chelating or inclusion agent covalently bonded to the surface thereof, and has one or more radioisotopes and/or one or more therapeutic agents either complexed with the hydrophilic chelating or inclusion agent or forms an inclusion compound with the hydrophilic chelating or inclusion agent on the surface of the stent, wherein the polymer layer is an outermost or exterior polymer layer on the surface of the stent.

* * * * *

EVIDENCE APPENDIX

EXHIBIT H

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,449	11/30/2001	Shamim M. Malik	050623.00134	3441

45159 7590 06/23/2009

SQUIRE, SANDERS & DEMPSEY LLP
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EXAMINER	
TYSON, MELANIE RUANO	
ART UNIT	PAPER NUMBER
3773	

MAIL DATE	DELIVERY MODE
06/23/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,449	MALIK ET AL.	
	Examiner	Art Unit	
	MELANIE TYSON	3773	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/13/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 13 May 2009 has been entered. Claims 2, 3, 7, 11, 12, and 14-30 are cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A single claim which claims both an apparatus (a stent having a plasma-polymerized polymer film layer) and the method steps of making the apparatus (wherein the plasma-polymerized polymer film is formed by exposing the stent to an acrylic acid plasma) is indefinite under 35 U.S.C. 112, second paragraph. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 5 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is rejected under 35 U.S.C. 101 based on the theory that the claim is directed to neither a "process" nor a "machine," but rather embraces or overlaps two different statutory classes of invention set forth in 35 U.S.C. 101, which is drafted so as to set forth the statutory classes of invention in the alternative only. See MPEP 2173.05(p).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-6, 8-10, 13, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (U.S. Patent No. 6,083,257 - cited on 892 dated 6/6/08), Ecer et al. (U.S. Patent No. 4,486,247 - cited on 892 dated 6/6/08), Narayanan et al. (U.S. Patent No. 5,336,518), and Kraus et al. (U.S. Patent No. 6,712,846 B1).

Taylor discloses a stent (see entire document) comprising a radially expandable metallic stent body formed of a stainless steel alloy (for example, see column 5, lines 51-56 and lines 62- 63) having a polymer film in intimate contact with the tissue contacting surface of the stent (for example see column 3, lines 63-67). Taylor fails to disclose the stent body comprises a carbon deposit.

Ecer discloses a stainless steel base material being modified by having carbon implanted within the surface of the stainless steel base material at a depth from about 300 to about 2500 angstroms, or of about 300 to about 1000 angstroms below the steel surface, which falls within the claimed range (for example, see column 1, lines 50-54 and 60-64). Ecer suggests that carbon is a known material for increasing the hardness of steel (for example, see column 1, lines 14-18). It is well known in the art that stainless steels having improved hardness yield stents having increased tensile strength, stiffness, and resistance to radial compression, thus improving the performance of the stent within, for example, a pulsating lumen. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide Taylor's stainless steel stent body with a carbon deposit as taught by Ecer in order to provide the stent with the advantages described above.

Taylor discloses the polymer film is applied to the stent surface by dipping methods, thus Taylor as modified by Ecer fails to disclose the polymer film layer is “chemically” bonded to the carbon deposit. Kraus discloses a polymer coated metallic stent (see entire document). Kraus teaches the polymer may be applied to the metallic stent by chemical vapor deposition (for example, see column 5, lines 39-41 and claim

27), thus chemically bonding the polymer film to the metallic stent. Thus, it would have been recognized by one of ordinary skill in the art that applying the known technique taught by Kraus to the metallic stent of Taylor as modified by Ecer would have yielded predicable results and resulted in an improved system, namely, a metallic stent with a carbon deposit having a polymer film chemically bonded thereto (i.e., to the stent including materials within the stent body such as the carbon deposit), thus reducing the risk of the film inadvertently coming off of the stent during handling and/or deployment.

Taylor also fails to disclose the polymer film is plasma polymerized. Narayanan discloses a metallic stent comprising a polymer film (see entire document). Narayanan teaches plasma polymerized films, such as HFBMA (which is an acrylate), to enhance metallic surfaces with permanent improved biocompatibility. Narayanan also teaches bioactive agents (or "therapeutic substance"; see claim 10 of the current application) formed on the plasma polymerized polymer film (for example, see column 3, lines 44-56), wherein the plasma-polymerized polymer film also provides a stronger bond with the bioactive agents, since covalent linkages are formed between the film and the agents (for example, see column 3, lines 34-44). It would have been obvious to one having ordinary skill in the art at the time the invention was made to form a therapeutic substance on Taylor's film layer as taught by Narayanan in order to enhance treatment and promote healing at the treatment site. Furthermore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to utilize a plasma polymerized polymer film in Taylor's invention as taught by Narayanan in order to provide the advantages described above. With further respect to claim 4, it would have

been obvious to one having ordinary skill in the art at the time the invention was made to provide a film layer comprising an acrylate material as taught by Narayanan, since it has been held to be within the general skill of a worker in the art to select a known material on the basis of its suitability for the intended use as a matter of design choice. With further respect to claim 6, Narayanan discloses the activated acrylate may comprise functional groups such as carboxy or amine (for example, see column 3, line 43 and 62-63).

For examination purposes, claim 5 is being treated as a product by process limitation, in that "the plasma-polymerized polymer film is formed by exposing the stent to an acrylic acid plasma" refers to the process of forming the plasma-polymerized polymer film and not to the final product created. As set forth in MPEP 2113, "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product in the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695,698,227 USPQ 964,966 (Fed. Cir. 1985). Examiner has evaluated the product claim without giving much weight to the method of its manufacture. Therefore, in this case, a plasma-polymerized polymer film formed by exposing the stent to an acrylic plasma is directed to the method of making the polymer film and not to the final product made. It appears that the product disclosed by Taylor as modified by Ecer, Kraus, and Narayanan would be the same, especially since both

applicant's product and the prior art product have the same final structure of a metallic stent having a plasma-polymerized polymer film layer.

Response to Arguments

Applicant's arguments with respect to the limitation "the plasma polymerized film layer is chemically bonded to the carbon deposit" and the Kamath et al. reference have been considered but are moot in view of the new ground(s) of rejection.

Applicant's arguments filed 13 May 2009 with respect to the Ecer reference have been fully considered but they are not persuasive. The applicant argues that Ecer fails to teach the carbon is deposited at a depth of not more than about 2000 angstroms beneath the surface of the stainless steel. However, it is the examiner's position that Ecer discloses such an embodiment (at a depth from about 300 to about 2500 angstroms, or of about 300 to about 1000 angstroms below the steel surface, which falls within the claimed range; for example, see column 1, lines 50-54 and 60-64).

The applicant further argues that the combination of Taylor and Ecer is improper. The applicant states that Ecer addresses solely the problem of friction and wear resistance, and the wear of Taylor's stent surface would not be an issue since Taylor's stent is entirely coated with a polymer layer. However, Ecer also addresses the problem of hardness and teaches that carbon is a known material for increasing the hardness of steel (for example, see column 1, lines 14-18). It is well known in the art that stainless steels having improved hardness yield stents having increased tensile strength, stiffness, and resistance to radial compression, thus improving the

performance of the stent within, for example, a pulsating lumen. Therefore, it is the examiner's position that the combination of Taylor and Ecer is proper.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELANIE TYSON whose telephone number is (571)272-9062. The examiner can normally be reached on Monday through Friday 7-7 (max flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jackie Ho can be reached on (571) 272-4696. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melanie Tyson/
Examiner, Art Unit 3773
June 18, 2009

EVIDENCE APPENDIX

EXHIBIT I

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,449	11/30/2001	Shamim M. Malik	50623.134	3441

45159 7590 12/16/2008

SQUIRE, SANDERS & DEMPSEY LLP
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SUITE 300
SAN FRANCISCO, CA 94111

EXAMINER	
TYSON, MELANIE RUANO	
ART UNIT	PAPER NUMBER
3773	

MAIL DATE	DELIVERY MODE
12/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,449	MALIK ET AL.	
	Examiner	Art Unit	
	Melanie Tyson	3773	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,8-10,13 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the applicant's amendment received on 08 September 2008. Claims 2, 3, 7, 11, 12, and 14-30 remain cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-6, 8-10, 13, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (6,083,257) in view of Ecer et al. (4,486,247), or in the alternative, over Taylor et al. in view of Ecer et al. and Kamath et al. (6,335,029).

Taylor discloses a stent (see entire document) comprising a metallic stent body formed of a stainless steel alloy (for example, see column 5, lines 51-56 and lines 62-63) having a polymer film (for example see column 3, lines 63-67).

Taylor fails to disclose the stent body comprises a carbon deposit. However, it is well known that stainless steel materials containing carbon implanted within the surface

as claimed enhances the strength and hardness of the stainless steel surface. Ecer discloses a stainless steel base material being modified by having carbon implanted within the surface of the stainless steel base material in order to enhance wear resistance (see detailed description of the Ecer et al. patent). It is well within the general knowledge of one having ordinary skill in the art to apply a known technique to a known device ready for improvement to yield predictable results. Therefore, it would have obvious to one having ordinary skill in the art at the time the invention was made to provide Taylor's stent body with a carbon deposit as taught by Ecer. Doing so would improve the stent's wear resistance. To further provide the carbon deposit such that it is present at a depth of not more than about 2000 A beneath the stent body surface would have been obvious to one having ordinary skill in the art at the time the invention was made, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art.

The limitation "plasma-polymerized" is being treated as a product by process limitation, in that "plasma-polymerized" refers to the process of depositing the polymer film layer to the stent and not to the final product created. As set forth in MPEP 2113, "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product in the prior art, the claim is unpatentable even though the prior product was made by a different process." In re

Thorpe, 777 F.2d 695,698,227 USPQ 964,966 (Fed. Cir. 1985). Examiner has evaluated the product claim without giving much weight to the method of its manufacture. Therefore, in this case, a stent as described above wherein the polymer film layer is plasma-polymerized over the stent body is directed to the method of making the stent and not to the final product made. It appears that the product disclosed by Taylor in view of Ecer would be the same or similar as that claimed; especially since both applicant's product and the prior art product have the same final structure of a metallic stent body having a carbon deposit and a polymer film layer.

In the alternative Kamath teaches applying a polymer film to a stent by a plasma polymerization process. Kamath teaches that this process allows covalent bonding between layers, thus subsequently offers a stronger adhesion (for example, see column 8, lines 37-44). It is well within the general knowledge of one having ordinary skill in the art to choose from a finite number of identified, predictable solutions, with a reasonable expectation of success. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to try depositing Taylor's in view of Ecer polymer film layer by a plasma polymerization process as taught by Kamath et al. Doing so would enhance the bond between the stent body and the polymer film. Since the plasma-polymerization process forms chemical bonds, the film layer would be chemically bonded to the stent body, including the carbon deposits.

With further respect to claims 4-6, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide the film layer with the materials claimed, since it has been held to be within the general skill of a worker in

the art to select a known material on the basis of its suitability for the intended use as a matter of design choice.

With further respect to claim 10, it would have been obvious to one having ordinary skill in the art at the time the invention was made to coat the stent with a polymeric layer comprising a therapeutic substance, since it is well known in the art to coat stents with drugs and agents in order to provide further treatment to the placement site. In the alternative, Kamath teaches forming a polymeric layer comprising a therapeutic substance formed on the plasma-polymerized film layer (see detailed description). It is well within the general knowledge of one having ordinary skill in the art to apply a known technique to a known device ready for improvement to yield predictable results. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide a polymeric layer comprising a therapeutic substance on the polymer film layer as taught by Kamath. Doing so would promote further healing to the treatment site.

Response to Arguments

Applicant's arguments filed 08 September 2008 have been fully considered but they are not persuasive. The applicant argues primarily that the prior art fails to disclose, teach, or suggest each and every element as claimed. Examiner respectfully disagrees.

The applicant argues primarily that since Kamath discloses a plasma polymerized polymer film applied to another layer that has been applied to the stent body, Kamath fails to disclose polymer coatings applied over a stent body surface. However, Taylor in

view of Ecer discloses a stent body having carbon deposits at a depth beneath the stent body surface and a polymer film deposited directly over the stent body surface (see rejection above). Kamath teaches that the process of depositing polymer films to stents by a plasma polymerization process is well known in the art in order to form chemical bonds between surfaces and thus enhancing bonds between surfaces (see rejection above). Even though Kamath teaches the process between films deposited over a stent body, Taylor in view of Ecer discloses the polymer film is deposited directly over the stent body surface. It is the examiner's position that to try applying the polymer film of Taylor in view of Ecer directly to the stent body surface by plasma-polymerization would have been obvious to one having ordinary skill in the art at the time the invention was made. Doing so may enhance the bond between the stent body surface and polymer film. Regarding the applicant's argument that Taylor and Kamath together make no mention of using carbon deposits in the metal stent for chemical bonding, it is the examiner's position that since plasma-polymerization forms chemical bonds, the process itself would form a chemical bond between the polymer film and stent body, including the carbon deposits, of the stent of Taylor in view of Ecer.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melanie Tyson whose telephone number is (571)272-9062. The examiner can normally be reached on Monday through Thursday 8:30-7 (max flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jackie Ho can be reached on (571) 272-4696. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Melanie Tyson /M. T./
Examiner, Art Unit 3773
November 20, 2008

/(Jackie) Tan-Uyen T. Ho/
Supervisory Patent Examiner, Art Unit 3773

EVIDENCE APPENDIX

EXHIBIT J

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:		Examiner:	
	Shamim M. Malik		Melanie Ruano Tyson
Serial No.:	09/997,449	Art Unit:	3773
Filed:	November 30, 2001	Confirmation No.:	3441
Customer No.:	45159	Attorney Docket No.:	050623.00134
Title:	A Modified Implantable Device Surface And A Method Of Making The Same		

Mail Stop **Amendment**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

Sir:

In response to the Non-Final Office Action dated June 23, 2009, please consider the following:

Amendments to the Claims are reflected in the listing of claims which begins on page 2.

Remarks begin on page 4.

An **Appendix** including a declarations under 37 CFR §1.132 follows page 12.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of the claims in the application:

Listing of Claims:

1. (Previously Presented) A stent comprising:

a metallic stent body having a stent body surface;

a molecular carbon deposit present at a depth of not more than about 2000 Å beneath the stent body surface; and

a plasma-polymerized polymer film layer deposited over the stent body surface and in intimate contact with the stent body surface, wherein the plasma-polymerized film layer is chemically bonded to the carbon deposit.

2. (Canceled)

3. (Canceled)

4. (Previously presented) The stent of Claim 1, wherein the plasma-polymerized polymer film layer comprises an acrylate.

5. (Previously presented) The stent of Claim 1, wherein the plasma-polymerized polymer film layer is formed by exposing the stent to an acrylic acid plasma.

6. (Previously presented) The stent of Claim 1, wherein the plasma polymerized film layer comprises functional groups selected from a group consisting of carboxylate, amine and sulfate.

7. (Canceled)

8. (Original) The stent of Claim 1, wherein the surface of the stent is the tissue-contacting surface of the stent.

9. (Previously presented) The stent of Claim 1, wherein the metallic stent body comprises stainless steel.

10. (Previously presented) The stent of Claim 1, further comprising a polymeric layer comprising a therapeutic substance formed on the plasma-polymerized polymer film layer.

11. – 12. (Canceled)

13. (Previously Presented) The stent of claim 1, wherein the metallic stent body comprises a radially expandable tubular body.

14. – 30. (Canceled)

31. (Previously presented) The stent of Claim 1, wherein the metallic stent body comprises an alloy.

REMARKS

Claims 1, 4 – 6, 8 – 10, 13 and 31 are currently pending. Claims 1, 4 – 6, 8 – 10, 13 and 31 have been rejected.

Reconsideration is respectfully requested.

Claim Rejections - 35 USC § 112 & 35 USC § 101

Rejection of Claim 5 under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claim 5 under 35 U.S.C. § 112, second paragraph as being indefinite. Specifically, it is the Examiner's view that "[a] single claim which claims both an apparatus (a stent having a plasma-polymerized polymer film layer) and the method steps of making the apparatus (wherein the plasma-polymerized polymer film is formed by exposing the stent to an acrylic acid plasma) is indefinite under 35 U.S.C. 112, second paragraph."

Rejection of Claim 5 under 35 U.S.C. § 101

The Examiner has also rejected claim 5 under 35 U.S.C. § 101. The Examiner has concluded that the claim is not statutory under 35 U.S.C. § 101 "based on the theory that the claim is directed to neither a 'process' nor a 'machine,' but rather embraces or overlaps two different statutory classes of invention set forth in 35 U.S.C. 101, which is drafted so as to set forth the statutory classes of invention in the alternative only." The Examiner has cited MPEP § 2173.05(p) to support this conclusion.

Applicants' Response

Applicants traverse both the 35 U.S.C. § 112, second paragraph and the 35 U.S.C. § 101 rejections of claim 5.

The Manual of Patent Examining Procedure (MPEP), 8th Edition, § 2173.05(p)(I) notes "[a] product-by-process claim, which is a product claim that defines the claimed product in terms of the process by which it is made, is proper." However, "[a] single claim which claims both an apparatus and the method steps of using the apparatus is indefinite under 35 U.S.C. 112, second paragraph," and "such claims may also be rejected under 35 U.S.C. 101 based on the theory that the claim is directed to neither a 'process' nor a 'machine,'. . . ." MPEP § 2173.05(p)(II) (citations omitted).

Claim 5 recites "[t]he stent of Claim 1, wherein the plasma-polymerized polymer film layer is formed by exposing the stent to an acrylic acid plasma," and claim 1 recites "[a] stent comprising . . . a plasma-polymerized polymer film layer deposited over the stent body surface . . . ." Claim 5 is not directed to an apparatus and a method of using the apparatus, but a product, and the process by which an element of the product is made. Thus, claim 5 is a proper product-by-process claim.

Applicants respectfully request the withdrawal of both the 35 U.S.C. § 101 and the 35 U.S.C. § 112 rejections of claim 5.

Additionally, applicants would like to point out that the claim 5 has remained substantially unchanged since amendment submitted in the Response of September 24, 2007 to the Office Action of April 25, 2007. Furthermore, claim 5 currently recites "[t]he stent of Claim 1, wherein the plasma-polymerized polymer film layer is formed by exposing the stent to an acrylic acid plasma," and claim 5 as filed recited "[t]he stent of claim 3, wherein the polymer is formed by exposing the stent to an acrylic acid plasma." As MPEP § 706 states "[t]he goal of examination is to clearly articulate any rejection early in the prosecution process so that the applicant has the opportunity to provide evidence of patentability and otherwise reply completely at the earliest opportunity," Applicants ask why the Examiner has not made these rejections until the present Office Action?

Claim Rejections - 35 USC § 103

The Examiner has rejected claims 1, 4 – 6, 8 – 10 , 13 and 31 under 35 U.S.C § 103(a) as being unpatentable over Taylor et al., United States Patent Application No. 6,083,257 (Taylor), Ecer et al., United States Patent Application No. 4,486,247 (Ecer), Narayanan et al. United States Patent Application No. 5,336,518 (Narayanan) and Kraus United States Patent Application No. 6,712,816 (Kraus).

The Examiner's Position

The Examiner has stated that Taylor discloses a metallic stent, in particular, a stent body of stainless steel, that is coated with a polymer coating, the polymer coating being in intimate contact with the tissue contacting surface of the stent.

The Examiner admits that Taylor does not disclose that the stent body has a carbon deposit. For the carbon deposits, the Examiner has cited Ecer. According to the Examiner, Ecer discloses "a stainless steel base material being modified by having carbon implanted within the surface of the stainless steel base material at a depth from about 300 to about 2500 angstroms, or of about 300 to about 1000 angstroms below the steel surface." Citing column 1, lines 14 – 18 of Ecer, the Examiner further contends that Ecer discloses "carbon is a known material for increasing the hardness of steel." The Examiner also states that "[i]t is well known in the art that stainless steels having improved hardness yield stents having increased tensile strength, stiffness, and resistance to radial compression, thus improving the performance of the stent within, for example, a pulsating lumen." Based upon the above, the Examiner has concluded that "it would have been obvious to one having ordinary skill in the art . . . to provide Taylor's stainless steel stent body with a carbon deposit as taught by Ecer in order to provide the stent with the advantages described above."

The Examiner further admits that the combination of Taylor as modified by Ecer fail to disclose "the polymer film layer is 'chemically' bonded to the carbon deposit." To cure this deficiency, the Examiner has cited Kraus, which in the Examiner's view teaches a polymer coated metallic stent, and "the polymer may be applied to the metallic stent by chemical vapor deposition, thus chemically bonding the polymer film to the metallic stent." Then, the Examiner concludes that one of skill in the art would have known to apply the known technique of Kraus to the metallic stent of Taylor as modified by Ecer to yield "predicable results and resulted in an improved system." According to the Examiner, the improved system would have been "a metallic stent with a carbon deposit having a polymer film chemically bonded thereto (i.e., to the stent including materials within the stent body such as the carbon deposit), thus reducing the risk of the film inadvertently coming off of the stent during handling and/or deployment."

The Examiner also admits that Taylor does not disclose that the polymer coating is plasma polymerized. Narayanan is thus cited for the alleged disclosure of a metallic stent and a polymer coating that may include bioactive agents. According to the Examiner, the coatings of Narayanan are "plasma polymerized films, such as HFBMA (which is an acrylate), to enhance metallic surfaces with permanent improved biocompatibility," and these plasma polymerized polymer films provide "a stronger bond with the bioactive agents, since covalent linkages are formed between the film and the Agents." According to the Examiner, one of skill in the art

would have added a bioactive agent to the coating of Taylor to "to enhance treatment and promote healing at the treatment site," and would have "utilize[d] a plasma polymerized polymer film in Taylor's invention as taught by Narayanan in order to provide the advantages described above."

With respect to the dependent claims, the Examiner also points to other portions of Narayanan as disclosing the elements of claims 4 and 6. Claim 5 has been treated as a product-by-process claim by the Examiner, and thus, it is obvious as "the product disclosed by Taylor as modified by Ecer, Kraus, and Narayanan would be the same" as Applicants' claim 5, "especially since both applicant's product and the prior art product have the same final structure of a metallic stent having a plasma-polymerized polymer film layer."

Applicants' Response

Applicants traverse the 35 U.S.C § 103(a) rejection as the Examiner has not established a *prima facie* case of obviousness for the following reasons:

(1) One of skill in the art would not have looked to Ecer as Ecer is non-analogous art

(2) If one of skill in the art had looked at Ecer, one would not have combined Taylor and Ecer as the Examiner has proposed

(3) If one had combined Ecer, Taylor, Kraus and Narayanan as the Examiner has proposed, an element, "the plasma-polymerized film layer is chemically bonded to the carbon deposit," is not present in the combination

(4) The Examiner has combined the references in an inconsistent manner

(5) The Examiner is using hindsight

(1) One of skill in the Art would not have looked to Ecer – Ecer is non-analogous art

Ecer is non-analogous art. As noted in MPEP § 2141.01, "to rely on a reference under 35 U.S.C. § 103, it must be analogous prior art." Ecer is directed to "steels having high wear resistance and low friction surfaces" and methods for producing such steels. Ecer provides that exemplary uses for such steels are "machines having components, each having surfaces . . . which are in sliding, lubricated contact with each other under a load . . . " (Ecer, column 3, lines 41 – 44). In the "Background" section of the patent, Ecer also discloses the following at column 1, lines 11 – 18:

> In the past, the wear resistance of steel surfaces has been improved by subjecting the steel to a high temperature process in which a wear resistant coating is bonded to the surface or an element such as, carbon and/or nitrogen, is thermally diffused into the steel surface to locally increase the hardness of the steel itself in a relatively wide layer extending inwardly from the steel surface.

As noted above, Ecer is directed to wear and abrasion resistance of metallic parts as evidenced by the title of the invention, "Wear resistant steel articles with carbon, oxygen and nitrogen implanted in the surface thereof," with the one reference to increasing the local hardness of steel by thermally diffusing carbon into the surface.

The Examiner has then taken the one statement in Ecer as the rationale for turning to Ecer. However, MPEP § 2141.02 states "[a] prior art reference must be considered in its entirety, i.e., as a whole, . . . " . *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)." The Examiner has taken the one statement out of context. When viewed as a whole, Ecer is clearly not in the same art as Applicants' claimed invention, that is, implantable medical devices. Further, Ecer does not address the same problem as Applicants' claims. Ecer addresses the problem of friction and wear resistance, which is in contrast to the problem that Applicants' invention addresses, the adherence of a polymeric layer to a metal substrate of an implantable medical device. When viewed as a whole, one of skill in the art would not have looked to Ecer as Ecer is directed to the issue of wear and abrasion resistance and is not in the field of medical devices.

(2) One of Skill in the Art would not have combined Taylor and Ecer

In contrast to her earlier position that one would have modified Taylor to improve wear resistance as taught by Ecer, the Examiner has now taken the position that one would have modified the metallic stent of Taylor using the method of Ecer to improve the mechanical properties, specifically the tensile strength, stiffness, and resistance to radial compression, of a stent. The Examiner has reached this conclusion based upon one statement in the background section of Ecer, that is ". . . an element such as, carbon and/or nitrogen, is thermally diffused into the steel surface to locally increase the hardness of the steel itself in a relatively wide layer extending inwardly from the steel surface" (column 1, lines 14 – 18) (emphasis added).

It is Applicants' position that one of skill in the art who was looking to solve the problem of increasing the tensile strength, stiffness, and resistance to radial compression, of a stent, and in

particular, a metallic stent, would not utilize the method of Ecer to achieve this goal. Clearly, Ecer refers to only locally increasing the hardness, that is at the surface. To support this position, in this response, Applicants submit the §132 Declarations of Dr. Pamela Kramer-Brown, who is not an inventor of the present application. Dr. Kramer-Brown is an employee of Abbott Cardiovascular Systems Inc., the assignee of the present application. Dr. Kramer-Brown works in research and development of stent materials, and particularly, metals. The declarations of Dr. Kramer-Brown supports Applicants' position that one of skill in the art would not have used the method disclosed by Ecer to improve the mechanical properties of a stent.

In sum, one of skill in the art would not have modified the stent of Taylor using the method of Ecer as suggested by the Examiner.

(3) The Combination of Ecer, Taylor, Kraus and Narayanan does not include all claim elements

As noted above, one of skill in the art would not have modified the stent body using the method of Ecer. However, even if one were to have modified the stent body of Taylor utilizing the method of Ecer as proposed by the Examiner with the result being a metallic stent body with carbon implanted at a depth from about 300 to about 2500 angstroms from the surface, the Examiner's further modification does not include all claim elements. The Examiner's has suggested that one of skill in the art would have further modified the combination of Taylor in view of Ecer by incorporating some of the teachings of Kraus and Narayanan. However, even with the additional modifications, "the plasma-polymerized film layer is chemically bonded to the carbon deposit," an element of claim 1, is missing from the combination.

The Examiner has cited Kraus for the purported disclosure of chemical bonding of the polymer film to the metallic stent. The Examiner has misinterpreted the reference. Kraus merely discloses that the polymer coating may be applied using chemical vapor deposition. Kraus does not disclose that the polymer coating is chemically or covalently bonded to the stent surface. Moreover, the disclosure of chemical vapor deposition does not inherently disclose the element. MPEP § 2112 provides the following criteria for a finding of inherency:

> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

Chemical vapor deposition is defined a process described as "the growth of thin solid films on a crystalline substrate as the result of thermochemical vapor-phase reactions" (www.answers.com/topic/chemical-vapor-deposition, from the sci-tech dictionary). There is nothing in the mere disclosure of chemical vapor deposition that necessarily requires that the coating so formed is chemically bonded to the surface. Furthermore, the Examiner has provided no explanation as to how she has arrived at the conclusion that chemical bonding is disclosed. The Examiner has done no more than point to a reference that discloses the formation a polymer coating on a stent by chemical vapor deposition, and then stated, without any further explanation, that chemical bonding would be present.

The Examiner has also cited Narayanan for the plasma polymerization of a polymer coating on the surface of a stent. There is no disclosure in Narayanan that the polymer coating formed chemically bonds to the substrate. Narayanan does disclose that there is covalent bonding between active agents included in the coating and the polymer coating. However, the covalent bonding of active agents to a polymer coating does not suggest or even hint at covalent or chemical bonding of a polymer coating to a metallic substrate.

In summary, there is no disclosure, suggestion, nor hint of chemical bonding of a polymer coating to a substrate in Ecer, Taylor, Kraus, or Narayanan, alone or in combination.

(4) The Examiner has combined the references in an inconsistent manner

As best understood by Applicants, the Examiner has proposed that one would have used the method of Ecer to modify the stent of Taylor to obtain a metallic stent body with implanted carbon, and further modification of the stent by using the polymer coating methods of Kraus and Narayanan. According to the Examiner, if the Taylor stent as modified by Ecer were coated using the method of Kraus, the result would be a polymer coating chemically bonded to the surface of the stent. Then the Examiner turns to Narayanan as disclosing the element "a plasma-polymerized polymer film layer," and thus concludes that one would use the plasma polymerization method of Narayanan to apply the polymer coating of Taylor. In the Examiner's view, Applicants claim 1 is therefore obvious in view of Taylor, Ecer, Kraus and Narayanan.

The Examiner's reasoning is inconsistent. If one were to use the chemical vapor deposition method of Kraus to apply the polymer coating instead of the dipping method of

Taylor to the stent, then in the Examiner's view, a view with which Applicants do not concur, the coating would be "chemically bonded to the surface." However, the coating would not be a "plasma-polymerized polymer film layer." On the other hand, if one were to use the plasma polymerization method of Narayanan instead of the dipping method of Taylor, the coating would meet the "plasma polymerized polymer film layer" element, but it would lack chemical bonding to the substrate.

Thus, as Applicant's best understand the Examiner's position, even without addressing any of the assumptions and conclusions that the Examiner has made, the combination of the four references as proposed by the Examiner does not meet all of the elements of claim 1.

(5) The Examiner is using hindsight

It appears that the Examiner is interpreting a finding of obviousness to require no more than citation to references ostensibly disclosing the individual elements. However, this is not the legal basis for obviousness. According to the Supreme Court,

> a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR International Co. v. Teleflex Inc. et al., 127 S. Ct. 1727, 1741 (2007). It is recognized that this precedent also holds that there need not be a specific teaching, suggestion or motivation in the art. However, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (citations omitted)(emphasis added).

In the present case, the Examiner has "found" the individual elements in different references, and then used convoluted reasoning to combine them such that the references, at least in the Examiner's opinion, read on Applicants' claim. None of the references disclose chemical bonding of a polymer coating to a stent surface. There is nothing in any of the four references, alone or in combination, that discloses or even hints at the implantation of carbon in the surface

of a stent to increase adhesion of a coating to the surface. The only reference even mentioning implantation of carbon, Ecer, is primarily directed to improving wear and abrasion resistance of metallic parts. It is only with reference to the teaching of Applicants' specification, that is Applicants' teaching of bonding of a layer to carbon deposits in the metallic body, that the Examiner has reached her conclusion. The fact that the Examiner has taken a single sentence from the background of Ecer as the rationale for the combination of Ecer with Taylor, has concluded that chemical bonding occurs based upon the mere recitation of chemical vapor deposition, and has combined the references in an inconsistent manner is evidence that Applicants' claimed invention is not obvious.

Conclusion

In light of the foregoing claim amendments and remarks, this application is considered to be in condition for allowance. Applicants respectfully request the allowance of pending claims 1, 4 – 6, 8 – 10, 13 and 31.

If necessary to ensure a timely response, this paper should be considered as a petition for an Extension of Time sufficient to provide a timely response. The undersigned authorizes the Commissioner to charge any fees that may be required, or credit of any overpayment to be made, to the **Squire, Sanders, and Dempsey Deposit Account No. 07-1850**.

Should the Examiner have any questions regarding this communication, the Examiner is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,

Dated: October 23, 2009

By /Gloria M. Gusler, Reg. No. 50,282/

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Reg. No. 50,282

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Appendix

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Shamim M. Malik, et al.	Examiner: Tyson, Melanie Ruano
Serial No. 09/997,449	Art Unit: 3773
Filed: November 30, 2001	Confirmation No.: 3441
Customer No.: 45159	Attorney Docket: 050623.00134
Title: A MODIFIED IMPLANTABLE DEVICE SURFACE AND A METHOD OF MAKING THE SAME	

Mail Stop: **Amendment**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration under 37 CFR § 1.132

I, Dr. Pamela Kramer-Brown, declare the following:

1. I received a Ph.D. in Materials Science Engineering from the University of California, Berkeley in 1998. I received an M.S. in Materials Science Engineering from the University of California, Berkeley in 1992 and a B.S. in Mechanical Engineering and Materials Science Engineering from the University of California, Berkeley in 1988.

2. I am currently employed by Abbott Vascular, formerly Advanced Cardiovascular Systems, Inc. (ACS), as an Advisor and Technical Manager on metallurgical materials research and development.

3. I was a Principal Engineer and Senior R&D Engineer at ACS from 1998 to 2005. My duties included research and development of stent materials. I was responsible for developing new materials, implementing key technology development methods, and contributing to the creation and revision of ASTM standards critical to the medical device industry.

4. I was a Graduate Researcher at E.O. Lawrence Berkeley National Laboratory from 1989 to 1998. My duties included research on aluminum alloys with discrete surface patterns and Sn/Pb materials containing low gold concentrations.

5. I was a Scientist Associate at Lockheed Missiles and Space Co. in 1989. I performed research on refractory metal alloys, as well as other projects related to materials science.

6. My professional affiliations include ASM International, ASTM, ISMRM, MRS, and TMS.

7. I am not an inventor of the current application, U.S. Patent Application Serial No. 09/997,449.

8. I have read and understand United States Patent No. 4,486,247 to Ecer et al. (Ecer).

9. I understand that Ecer discloses a method of implanting carbon into a steel surface to a depth of about 2500 Angstroms.

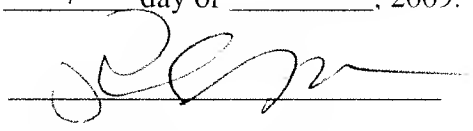
10. I understand that the method disclosed in Ecer is directed to providing "a low friction, high wear resistance surface layer" to improve the wear resistance of the steel.

11. I submit that if I, as a person of skill in the art, were trying to achieve the goal of increasing the tensile strength, stiffness, and resistance to radial compression of a stent, I would not use the carbon implantation method of Ecer on a stainless steel stent body to achieve this goal.

12. I submit that I expect that if the method of Ecer were used on a stainless steel stent body, no significant improvement in the tensile strength, stiffness, and resistance to radial compression of the stent would be observed because the carbon is implanted near the surface of the stent, and would not result in a change in properties in the vast majority of the stent body.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed at **Santa Clara**, California on this 14 day of October, 2009.



Dr. Pamela Kramer-Brown

EVIDENCE APPENDIX

EXHIBIT K

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Shamim M. Malik, et al.	Examiner: Tyson, Melanie Ruano
Serial No. 09/997,449	Art Unit: 3773
Filed: November 30, 2001	Confirmation No.: 3441
Customer No.: 45159	Attorney Docket: 050623.00134
Title: A MODIFIED IMPLANTABLE DEVICE SURFACE AND A METHOD OF MAKING THE SAME	

Mail Stop: **Amendment**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration under 37 CFR § 1.132

I, Dr. Pamela Kramer-Brown, declare the following:

1. I received a Ph.D. in Materials Science Engineering from the University of California, Berkeley in 1998. I received an M.S. in Materials Science Engineering from the University of California, Berkeley in 1992 and a B.S. in Mechanical Engineering and Materials Science Engineering from the University of California, Berkeley in 1988.

2. I am currently employed by Abbott Vascular, formerly Advanced Cardiovascular Systems, Inc. (ACS), as an Advisor and Technical Manager on metallurgical materials research and development.

3. I was a Principal Engineer and Senior R&D Engineer at ACS from 1998 to 2005. My duties included research and development of stent materials. I was responsible for developing new materials, implementing key technology development methods, and contributing to the creation and revision of ASTM standards critical to the medical device industry.

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7. I am not an inventor of the current application, U.S. Patent Application Serial No. 09/997,449.

8. I have read and understand United States Patent No. 4,486,247 to Ecer et al. (Ecer).

9. I understand that Ecer discloses a method of implanting carbon into a steel surface to a depth of about 2500 Angstroms.

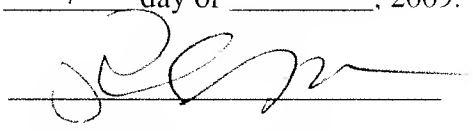
10. I understand that the method disclosed in Ecer is directed to providing "a low friction, high wear resistance surface layer" to improve the wear resistance of the steel.

11. I submit that if I, as a person of skill in the art, were trying to achieve the goal of increasing the tensile strength, stiffness, and resistance to radial compression of a stent, I would not use the carbon implantation method of Ecer on a stainless steel stent body to achieve this goal.

12. I submit that I expect that if the method of Ecer were used on a stainless steel stent body, no significant improvement in the tensile strength, stiffness, and resistance to radial compression of the stent would be observed because the carbon is implanted near the surface of the stent, and would not result in a change in properties in the vast majority of the stent body.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed at **Santa Clara**, California on this 14 day of October, 2009.



Dr. Pamela Kramer-Brown

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.:	09/997,449
Applicant:	Shamim M. Malik *et al.*
Filed:	November 30, 2001
Art Unit:	3773
Examiner:	Melanie R. Tyson
Docket No.:	050623.00134
Confirmation No.:	3441
Customer No.:	45159
Title:	A Modified Implantable Device Surface And A Method Of Making The Same

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Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir:

This Appeal Brief is submitted pursuant to the Notice of Appeal that was filed on 24 June 2011 in response to the Final Rejection mailed on 04 April 2011 in which the Examiner reiterated the rejections of the 31 August 2010 Non-Final Office Action, rejecting all pending claims in the application.

I. REAL PARTY IN INTEREST

The real party in interest with regard to this appeal is Abbott Cardiovascular Systems Inc., with its primary place of business at 3200 Lakeside Drive, Santa Clara, California 95054. The present application was filed on November 30, 2001. The assignment of application serial no. 09/997,449 to Advanced Cardiovascular Systems, Inc., was recorded in the United States Patent and Trademark Office on November 30, 2001, in Reel 012339, at Frame 0808. Abbott Cardiovascular Systems Inc. purchased the vascular device division and all relevant intellectual property including the instant application of Advanced Cardiovascular Systems, Inc. (Guidant Corporation) in May 2006.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' assignee, and their counsel are not aware of any related appeals or interferences which would affect, be affected by, or have a bearing on the instant appeal.

III. STATUS OF CLAIMS

Claims 2, 3, 7, 11, 12, and 14 – 30 have been cancelled without prejudice to reclaiming the subject matter therein in a subsequent application.

Claims 1, 4 – 6, 8 – 10, 13, and 31 have been finally rejected and are the subjects of this appeal.

IV. STATUS OF AMENDMENTS

There are no unentered amendments.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The appealed application contains one independent claim, claim 1. The support for claim 1 can be found in the specification. Independent claim 1[1] is directed to a stent. (specification paragraph [0001]) The stent includes a metallic stent body having a stent body surface. (specification paragraphs [0006] and [0013]) The stent also includes a molecular carbon deposit present at a depth of not more than about 2000 Å beneath the stent body surface. (specification paragraph [0015]) The stent also includes a plasma-polymerized polymer film layer deposited over the stent body surface and in intimate contact with the stent body surface. (specification paragraph [0021] and Figure 2C) The

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[1] 1. A stent comprising:

a metallic stent body having a stent body surface;

a molecular carbon deposit present at a depth of not more than about 2000 Å beneath the stent body surface; and

a plasma-polymerized polymer film layer deposited over the stent body surface and in intimate contact with the stent body surface, wherein the plasma-polymerized film layer is chemically bonded to the carbon deposit.

plasma-polymerized film layer is chemically bonded to the carbon deposit. (specification paragraph [0019])

Dependent claims 4 – 6, 8 – 10, 13, and 31 depend from claim 1.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The ground for rejection to be reviewed in this appeal is:

Whether claims 1, 4 – 6, 8 – 10, 13, and 31 are rendered obvious, and are therefore unpatentable under 35 U.S.C. § 103(a), by Taylor *et al.*, United States Patent No. 6,083,257 (Evidence Appendix, Exhibit A) (Taylor), in view of Ecer *et al.*, United States Patent No. 4,486,247 (Evidence Appendix, Exhibit B) (Ecer), and further in view of Narayanan *et al.*, United States Patent No. 5,336,518 (Evidence Appendix, Exhibit C) (Narayanan).

VII. ARGUMENTS

Claims 1, 4 – 6, 8 – 10, 13, and 31 are patentable under 35 U.S.C. § 103(a) over Taylor, in view of Ecer, and further in view of Narayanan.

The Examiner's Contentions:

In the Final Office Action of 04 April 2011 (Evidence Appendix, Exhibit D) (April 2011 Final Office Action), the Examiner has maintained her rejection of claims 1, 4 – 6, 8 – 10, 13, and 31 over Taylor, in view of Ecer, and further in view of Narayanan that was made in the Non-Final Office Action of 31 August 2010 (Evidence Appendix, Exhibit E) (August 2010 Non-Final Office Action).

The August 2010 Non-Final Office Action was issued in response to an Appeal Brief filed by Appellants on 24 June 2010 pursuant to a Notice of Appeal filed on 24 March 2010. Appellants filed the Notice of Appeal on 24 March 2010 in response to the Final Office Action of 24 December 2009 (Evidence Appendix, Exhibit F) (December 2009 Final Office Action), in which the Examiner maintained her rejection of claims 1, 4 – 6, 8 – 10, 13, and 31 over Taylor, in view of Ecer, and further in view of Narayanan and Kraus *et al.*, United States Patent No. 6,712,816 (Evidence Appendix, Exhibit G) (Kraus), that the Examiner had made in the Office Action of 23 June 2009 (Evidence Appendix, Exhibit H) (June 2009 Office Action).

The Examiner has alleged that Taylor discloses a metallic stent, in particular, a stent body of stainless steel, which is coated with a polymer coating, the polymer coating being in intimate contact with the tissue contacting surface of the stent.

The Examiner has admitted that Taylor does not disclose that the stent body has a carbon deposit. For the carbon deposits, the Examiner has cited Ecer. According to the Examiner, Ecer discloses "a stainless steel base material being modified by having carbon implanted within the surface of the stainless steel base material at a depth from about 300 to about 2500 angstroms, or of about 300 to about 1000 angstroms below the steel surface." With citation to column 1, lines 14 – 18 of Ecer, the Examiner has further made the contention that Ecer discloses "carbon is a known material for increasing the hardness of steel." The Examiner has also stated that "[i]t is well known in the art that stainless steels having improved hardness yield stents having increased tensile strength, stiffness, and resistance to radial compression, thus improving the performance of the stent within, for example, a pulsating lumen." Based upon the above, the Examiner has

concluded that "it would have been obvious to one having ordinary skill in the art . . . to [have] provide[d] Taylor's stainless steel stent body with a carbon deposit as taught by Ecer in order to provide the stent with the advantages described above."

The Examiner has admitted that "Taylor as modified by Ecer fails to disclose the polymer film layer comprises an acrylate and is chemically bonded to the carbon deposit." Therefore, the Examiner has cited Narayanan to cure these deficiencies. According to the Examiner, "Narayanan discloses a metallic stent comprising a polymer film," and also that the films ". . . containing acrylate, such as HFBMA, enhance metallic surfaces with permanent improved biocompatibility." The Examiner has then concluded that one of skill in the art would have applied the acrylate film as taught by Narayanan for improved biocompatibility. With respect to the covalent bonding to the carbon deposits, the Examiner has cited Appellants' specification, which, in the Examiner's view, discloses " . . . that depositing films to stents via plasma polymerization deposition is well known in the art," and also that "'one having ordinary skill in the art will recognize that some fragmentation of the acrylate typically occurs during the plasma polymerization deposition of the film layer, resulting in an acrylate-like polymer layer of fragmented acrylate, which will be covalently bonded to carbon deposits.'" Thus, the Examiner has concluded that the use of a plasma polymerization process to apply a polymer film "would yield a device in which the polymer film layer is covalently bonded to the carbon deposit as recited in the claims."

The Examiner has also reiterated her position that claim 5 is treated as a product-by-process claim, and therefore the Examiner has not given much weight to the method of manufacture. With respect to claim 6, the Examiner has taken the position that

"Narayanan discloses the activated acrylate may comprise functional groups such as carboxylate or amine," where the Examiner has cited column 3, lines 43, 62, and 63 of Narayanan to support this position.

Regarding claim 10, the Examiner has also alleged that "Narayanan also teaches bioactive agents formed on the plasma polymerized polymer film . . . ," and therefore, one would have formed ". . . a therapeutic substance on the modified film layer above as taught by Narayanan in order to enhance treatment and promote healing at the treatment site."

Appellants' Response

Claims 1, 4 – 6, 8 – 10, 13, and 31 are patentable under 35 U.S.C. § 103(a) over Taylor, in view of Ecer, and further in view of Narayanan.

The Examiner has not established a *prima facie* case of obviousness for the following reasons:

(1) One of skill in the art would not have looked to Ecer as Ecer is non-analogous art

(2) If one of skill in the art had looked at Ecer, one would not have combined Taylor and Ecer as the Examiner has proposed

(3) The Examiner is using hindsight

(1) One of skill in the Art would not have looked to Ecer – Ecer is non-analogous art

Ecer is non-analogous art. As noted in the Manual of Patent Examining Procedure (MPEP), 8th Edition, § 2141.01, "to rely on a reference under 35 U.S.C. § 103, it must be analogous prior art." Ecer is directed to "steels having high wear resistance and low friction surfaces" and methods for producing such steels. Ecer provides that exemplary uses for such steels are "machines having components, each having surfaces . . . which are in sliding, lubricated contact with each other under a load . . . ." (Ecer, column 3, lines 41 – 44) In the "Background" section of the patent, Ecer also discloses the following at column 1, lines 11 – 18:

> In the past, the wear resistance of steel surfaces has been improved by subjecting the steel to a high temperature process in which a wear resistant coating is bonded to the surface or an element such as, carbon and/or nitrogen, is thermally diffused into the steel surface to locally increase the hardness of the steel itself in a relatively wide layer extending inwardly from the steel surface.

As noted above, Ecer is directed to wear and abrasion resistance of metallic parts as evidenced by the title of the invention, "Wear resistant steel articles with carbon, oxygen and nitrogen implanted in the surface thereof," with the one reference to increasing the local hardness of steel by thermally diffusing carbon into the surface.

The Examiner has then taken the one statement in Ecer as the rationale for the citation of Ecer. However, MPEP § 2141.02 recites "'[a] prior art reference must be considered in its entirety, i.e., as a whole, ...' *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)." The Examiner has taken the one statement out of context. When viewed as a

whole, Ecer is clearly not in the same art as Appellants' claimed invention, that is, implantable medical devices. Further, Ecer does not address the same problem as Appellants' claims. Ecer addresses the problem of friction and wear resistance, which is in contrast to the problem that Appellants' claimed invention addresses, the adherence of a polymeric layer to a metal substrate of an implantable medical device. When viewed as a whole, one of skill in the art would not have looked to Ecer as Ecer is directed to the issue of wear and abrasion resistance and is not in the field of medical devices.

In response to Appellants' arguments, the Examiner had previously stated, in the August 2010 Non-Final Office Action, that ". . . medical devices are formed of different materials in which wear and abrasion resistance are concerns of medical devices implanted within the body." (August 2010 Non-Final Office Action, page 3, lines 5 – 7) In the April 2011 Final Office Action, the Examiner has made no comments at all regarding the fact that Ecer is not directed to medical devices. Appellants again fail to see the relevance of methods of improving wear and abrasion resistance of a metallic surface to the situation in which the metallic surface is to be coated with a polymer.

(2) One of Skill in the Art would not have combined Taylor and Ecer

Earlier in the prosecution of the present application, specifically at least in the Final Office Action of 16 December 2008 (Evidence Appendix, Exhibit I) (December 2008 Final Office Action), the Examiner took the position that that one would have modified Taylor to improve wear resistance as taught by Ecer. In contrast to this earlier position, the Examiner has now taken the position that one would have modified the metallic stent of Taylor using the method of Ecer to improve the mechanical properties,

specifically the tensile strength, stiffness, and resistance to radial compression, of a stent. The Examiner has reached this conclusion based upon one statement in the background section of Ecer, that is ". . . an element such as, carbon and/or nitrogen, is thermally diffused into the steel surface to locally increase the hardness of the steel itself in a relatively wide layer extending inwardly from the steel surface." (Ecer, column 1, lines 14 – 18) (emphasis added)

It is Appellants' position that one of skill in the art seeking to solve the problem of increasing the tensile strength, stiffness, and resistance to radial compression, of a stent, and in particular, a metallic stent, would not have utilized the method of Ecer as a means of achieving this goal. Clearly, Ecer only refers to locally increasing the hardness, or in other words, increasing the hardness at the surface. To support this position, in the 23 October 2009 Response (Evidence Appendix, Exhibit J) (October 2009 Response) to the June 2009 Non-Final Office Action, Appellants submitted the §132 Declaration of Dr. Pamela Kramer-Brown (Evidence Appendix, Exhibit K) (Declaration), who is not an inventor of the present application. Dr. Kramer-Brown is an employee of Abbott Cardiovascular Systems Inc., the owner of the present application. Dr. Kramer-Brown works in research and development of stent materials, and particularly, metals. The declaration of Dr. Kramer-Brown supports Appellants' position that one of skill in the art would not have used the method disclosed by Ecer to improve the mechanical properties of a stent.

In the Response to Arguments in the December 2009 Final Office Action, the Examiner stated that the totality of evidence of nonobviousness fails to outweigh the evidence of obviousness. Moreover, with respect to the combination of Taylor and Ecer,

in the Response to Arguments (December 2009 Final Office Action, page 7, lines 5 – 7), the Examiner took the position that "since some improvement may be observed, it is the examiner's position one having ordinary skill in the art may look to Ecer to modify Taylor to achieve such improvement." In the April 2011 Final Office Action, the Examiner has proffered yet another rationale for the combination of Taylor and Ecer. The Examiner has stated that "since at least a local increase in hardness is achieved, it is the examiner's position [that] one having ordinary skill in the art would look to Ecer to modify Taylor to achieve such improvements throughout the stent." (April 2011 Final Office Action, page 2 and 3) It appears that the Examiner has ignored, and/or has completely discounted, the statement in the Declaration that if one were trying to achieve the goals of increasing the tensile strength and stiffness of a stent, and the stent's resistance to radial compression, the method of Ecer would not be used to achieve these goals. The Examiner's failure to consider the Declaration is improper.

In sum, one of skill in the art would not have modified the stent of Taylor using the method of Ecer as has been suggested by the Examiner. Furthermore, Narayanan does not cure the deficiency of Taylor and Ecer with respect to the claims.

(3) The Examiner is using hindsight

It appears that the Examiner has interpreted a finding of obviousness to require no more than citation to references ostensibly disclosing the individual elements. However, this is not the legal basis for obviousness. According to the Supreme Court,

> a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR International Co. v. Teleflex Inc. et al., 127 S. Ct. 1727, 1741 (2007) It is recognized that this precedent also holds that there need not be a specific teaching, suggestion or motivation in the art. However, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (citations omitted)

In the present case, the Examiner has "found" the individual elements in different references, and then has used convoluted and continually changing reasoning to combine them, such that the references, at least in the Examiner's opinion, read on Appellants' claims. The only reference even mentioning implantation of carbon, Ecer, is primarily directed to improving wear and abrasion resistance of metallic parts. The fact that the Examiner has taken a single sentence from the background of Ecer as the rationale for the combination of Ecer with Taylor is evidence that Appellants' claims are not obvious. Narayanan does not cure the deficiency of Taylor and Ecer with respect to claim 1. As a result, claim 1, and claims depending from claim 1, are not rendered obvious by Taylor, Ecer, and Narayanan, either individually, or in combination.

CONCLUSION

The Examiner has failed, as a matter of law, to set forth a case of unpatentability of claims 1, 4 – 6, 8 – 10, 13, and 31. Appellants therefore respectfully request that the Board reverse the Examiner's rejection and order that the application proceed to issue.

The Commissioner is hereby authorized to charge the **Squire, Sanders & Dempsey (US) LLP Deposit Account No. 07-1850** for any fees due.

Respectfully submitted,

Date: Wednesday, August 24, 2011

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VIII. CLAIMS APPENDIX

Listing of Claims:

1. A stent comprising:

a metallic stent body having a stent body surface;

a molecular carbon deposit present at a depth of not more than about 2000 Å beneath the stent body surface; and

a plasma-polymerized polymer film layer deposited over the stent body surface and in intimate contact with the stent body surface, wherein the plasma-polymerized film layer is chemically bonded to the carbon deposit.

2. (Cancelled)

3. (Cancelled)

4. The stent of Claim 1, wherein the plasma-polymerized polymer film layer comprises an acrylate.

5. The stent of Claim 1, wherein the plasma-polymerized polymer film layer is formed by exposing the stent to an acrylic acid plasma.

6. The stent of Claim 1, wherein the plasma polymerized film layer comprises functional groups selected from a group consisting of carboxylate, amine and sulfate.

7. (Cancelled)

8. The stent of Claim 1, wherein the surface of the stent is the tissue-contacting surface of the stent.

9. The stent of Claim 1, wherein the metallic stent body comprises stainless steel.

10. The stent of Claim 1, further comprising a polymeric layer comprising a therapeutic substance formed on the plasma-polymerized polymer film layer.

11. (Cancelled)

12. (Cancelled)

13. The stent of claim 1, wherein the metallic stent body comprises a radially expandable tubular body.

14. – 30. (Cancelled)

31. The stent of Claim 1, wherein the metallic stent body comprises an alloy.